(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 July 2004 (15.07.2004)

PCT

(10) International Publication Number
WO 2004/058265 A1

(51) International Patent Classification[7]: A61K 31/4965, 31/497, C07D 241/24, 241/20, 241/22, 403/04, 401/12, 403/10, 413/12, C07B 61/00

(21) International Application Number: PCT/GB2003/005668

(22) International Filing Date: 24 December 2003 (24.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0230195.0 24 December 2002 (24.12.2002) GB

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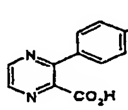
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOUND LIBRARIES OF 2,3-SUBSTITUTED PYRAZINE DERIVATIVES CAPABLE OF BINDING TO G-PROTEIN COUPLED RECEPTORS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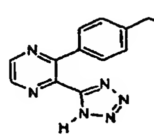
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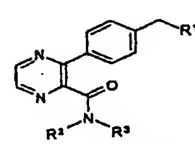
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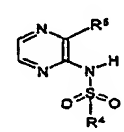
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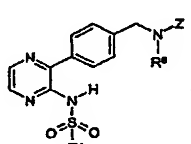
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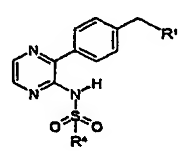
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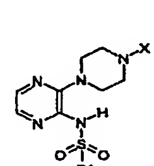
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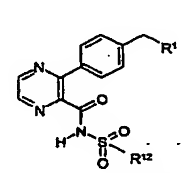
(F)

(57) Abstract: The present invention provides a compound library designed to pick up interactions with receptors for a subset of peptidic receptors, especially those with recognition sites for amide and acidic ligands based around TM3 and TM6. The presence of the amide-acid recognition site here is a consequence of the requirements for binding the natural ligands either with C-terminal regions or with the backbone of peptide loops. The library comprises or consists of a set of structurally related compounds of the following general formulae; formula (A) formula (B) formula (C) formula (D1).

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COMPOUNDS LIBRARIES OF 2,3-SUBSTITUTED PYRAZINE DERIVATIVES CAPABLE OF BINDING TO G-PROTEIN COUPLED RECEPTORS

Introduction

Background

The present invention relates to compounds capable of binding to G-protein coupled receptors. In particular, a library of compounds is provided for use in screening programmes against GPCR targets as well as the individual compounds for use in hit to lead and lead optimisation projects and similar stages in the drug discovery process.

The method also provides methods for making compounds and libraries.

As part of the process of discovering drugs or agrochemicals it is customary to screen libraries of compounds against biological targets to discover 'Hits' which are then further developed into 'Leads' and subsequently drugs or agrochemicals by using the techniques of medicinal chemistry. Accordingly the success or not of a drug or agrochemical discovery project is critically dependent on the quality of the hit and this in turn is dictated by the quality of the screening library.

Technological advances have enabled screening on a very large scale and the screening of hundreds of thousands of compounds at the start of a discovery program is routine. This, however, does entail a significant cost. The hits obtained from such screening efforts are not all of the best quality and often take a large amount of subsequent time and effort in order to get a good lead. It has been

estimated that only about 25% of projects actually get to the lead optimisation stage and part of the reason for this is the intractability of hits from high throughput screening.

Screening libraries are commonly collections of compounds from several sources. As a result, they typically contain compounds synthesised as a part of previous projects in the history of a company. With regard to drug discovery, these collections will be drug-like but are likely to be limited in scope and will be directed to certain areas of a particular project. It has been the common practice of many pharmaceutical companies in recent times to augment the collections by purchasing either single compounds from vendors or by contracting the synthesis of combinatorial libraries of compounds. The singly purchased compounds may have been selected to fill in areas of compound space poorly represented in the compound collections. Combinatorial libraries are typically synthesised around well-performing chemistries with some design based on producing 'diversity' in compound space.

A complementary approach, and one that is increasingly preferred, is to screen focused libraries against the target of choice. Focused libraries are becoming of increasing importance in their ability to generate hits capable of rapid expansion in many areas including GPCRs. Such libraries are slightly more expensive to prepare but have attributes of reliability, reproducibility and provide a considerably higher hit rate: typically 10-100 fold and above compared with random screening. They are, however, very difficult to design and their efficiency relates directly to the amount of effort that has gone into the design. Using focused libraries, it is usually

possible to get a number of hits in the low micromolar and below range. As there is a defined set of compounds there is the potential to observe indications of SAR in a chemical series and progress the chemistry efficiently.

G-protein-coupled receptors (GPCRs) are very important in the regulation of numerous body processes and a significant proportion of all drugs work by interaction with these receptors. There are several hundred known, many of which are orphans - those receptors that have no established ligands. They fall into a class of 7-transmembrane receptors and there is only one X-ray structure known that of the bovine rhodopsin receptor, and this is at a resolution of 2.8 Angstroms and is thus not suitable for accurate modeling work. In addition, the rhodopsin receptor is somewhat unusual in its interactions with its ligand and is not used as a drug target. Nevertheless the overall three dimensional arrangement can be deduced from the X-ray and is in accordance with previous work based upon bacteriorhodopsin receptor which is not G-protein-coupled.

GPCRs are most often characterised by sequence homology as being comprised of several sub-families. Most attention currently is directed towards Family A receptors as being the most tractable class historically and also the one with the most potential targets.

Family A comprises about 300 receptors that are potential drug targets, approximately half of which have known ligands and the rest, the so-called orphan receptors. The group of druggable receptors is composed essentially of two types: those whose natural ligand interacts wholly within the transmembrane domain, such as the aminergic,

nucleotide-like, prostaglandin receptors, etc. and those peptide liganded receptors, which have a large part of their interactions in the extracellular region and which may insert a peptide loop or tail into the transmembrane region to effect signal transduction. Examples of this class are angiotensin, cholecystokinin and opioid receptors. Irrespective of the mode of action of the natural ligand or the GPCR family, the vast majority of drug molecules interact in the all-helical domain of the transmembrane region with exceptions being those mimics of glutamate at the metabotropic glutamate receptor and some peptide therapeutics administered parenterally. In looking for lead molecules for an unexplored or orphan GPCR it therefore makes sense to concentrate on interactions in the transmembrane domain.

The focused library provided herein is designed to interact with a range of the family A receptors. Each library is a defined set of compounds that will enhance the probability of finding a small molecule that will interact with one or more type of GPCR receptor.

For example, focused libraries can be provided having compounds which will interact with aminergic GPCRs, and peptidic GPCRs requiring an obligatory positive charge in ligands, or other types or groups of GPCRs.

Focused libraries according to this invention can provide hit rates of 1-13% or more for the requisite predicted GPCRs from both amine- and peptide-liganded classes and with agonists and antagonists.

Summary of Invention

We provide herein a "focused" library of compounds which will provide "leads" for ligands which bind to Family A G-Protein coupled receptors.

In the context of the present invention, "library" means a group of compounds which are structurally related by virtue of a core chemical structure (or "scaffold") but which differ from each other by virtue of permutation of specific substituent groups attached to the scaffold.

Generally speaking such a library will consist of or comprise a number of compounds, e.g. as many as about 100, 1000,2000, 3000 or indeed 10,000 compounds. The number of compounds should be sufficient to provide an adequate diversity of related compounds without being so large as to be unduly complex/expensive to produce.

In the context of the present invention the terms "permitted substituents" and analogous terms are used to refer to defined chemical groups that may be attached to a "scaffold" to provide permutations of the chemical structure of related compounds.

Where the chemical formulae of permitted substituents are shown in this description and claims, the substituent may appear in the compound exactly as shown (i.e. simply covalently bonded to the scaffold) or may be a derivative of the shown chemical formula of the substituent by virtue of use of a reactive group to couple the substituent to the scaffold.

It will be appreciated that the total number of permutations created by the permitted substituents may be a very large number, far greater in magnitude than the actual number of compounds in an actual library. In other words, the number of possible compounds for any "virtual" library may well greatly exceed the number of synthesised compounds making up an embodiment of the "real" library. The invention is intended to encompass libraries having all, and a number, which is less than all, of the permitted substitutions represented by compounds therein.

It will be appreciated that some specific combinations of permitted substituents may be more or less difficult to synthesise and/or use in a focused library of the invention. This does not detract from the generality of applicability of the invention as described herein. It is to be expected that real libraries will be synthesised from a selected group of permutations/combinations of permitted substituents, taking into consideration factors affecting the intended purpose of the library and its cost and complexity of synthesis.

Even if theoretically permitted, it is currently considered unlikely that any compound would be prepared for inclusion in a focused library if it had either or both of the following properties

(1) molecular weight >700

(2) log p <-3 or >9 (an index of lipophilicity as calculated using commercially available "Chemenlighten 2.8" and "Biobyte" software for the log p calculation).

The present invention provides a novel focused library of compounds. Most of the compounds defined by the permitted substitutions on the scaffolds are also novel compounds per se and the invention is intended to encompass each individual novel compound.

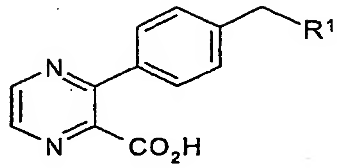
International application WO 03/00308 discloses a compound library suitable for use in identifying compounds which act on G-protein coupled receptors, also called 7TM receptors. This compound library may overlap with WO 03/00308, but is not identical to the compound library of the present invention. Where compounds per se are claimed by the present invention, generally any compounds specifically claimed in WO 03/00308 are hereby disclaimed per se.

Any known compound having a structural formula identical to any one of the compounds covered by the formulae of scaffolds and permitted substitutions described herein is hereby explicitly disclaimed per se.

Description of the Invention Library 5

Library 5 is designed to pick up interactions with receptors for a subset of peptidic receptors, especially those with recognition sites for amide and acidic ligands based around TM3 and TM6. This group is represented by such receptors as Bombesin (BSR3), Endothelin A, Neuromedin U and Neuropeptide Y amongst others. The presence of the amide-acid recognition site here is a consequence of the requirements for binding the natural ligands either with C-terminal regions or with the backbone of peptide loops. The techniques used in designing this library have also provided the opportunity to design both agonists and antagonists for these receptors.

The invention provides a compound library comprising of a set of structurally related compounds of the following general formulae:



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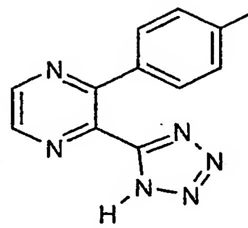

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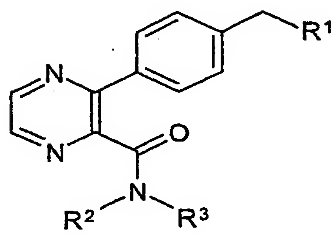

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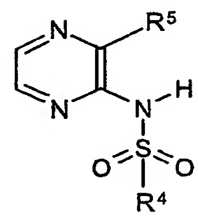

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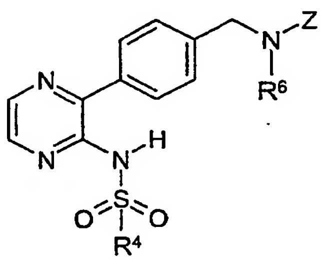

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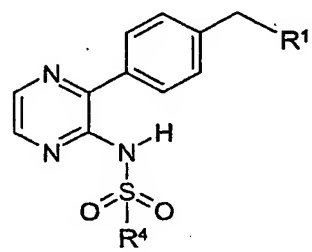
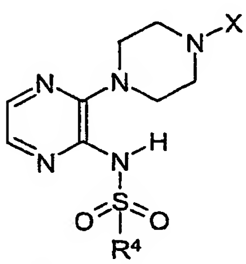


(D3)



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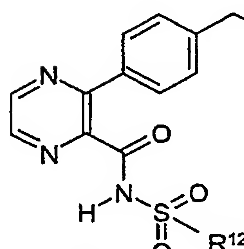

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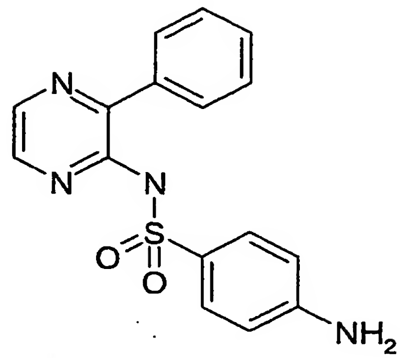
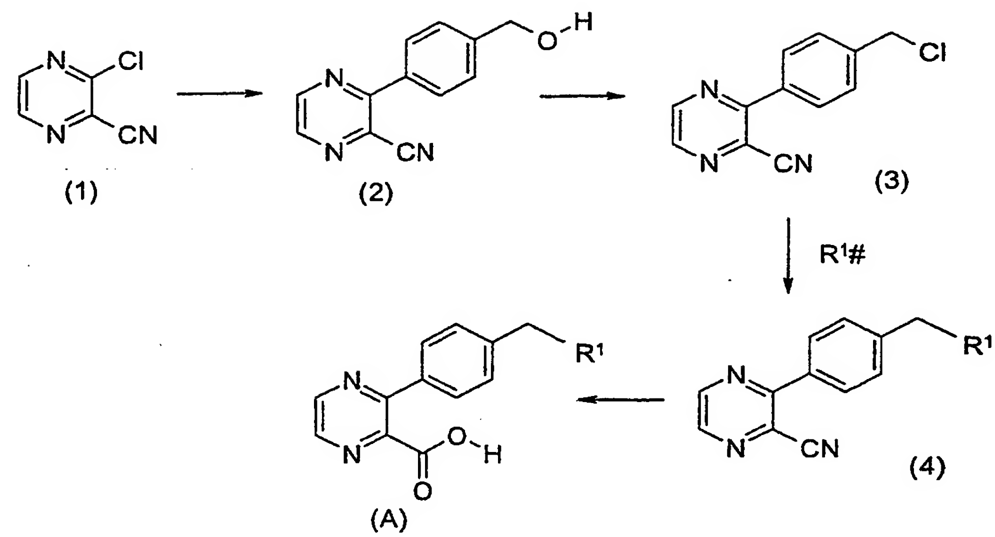
Structural Novelty of Compounds of Library 5

Where aryl pyrazine compounds of library 5 form an isolated ring, the following compound is known:



Methods of Synthesising Compounds of Formula A (Scheme 1)

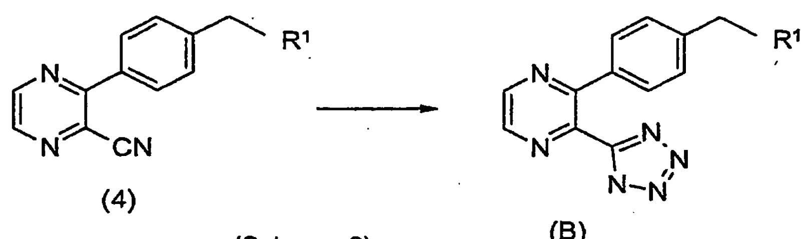
Compounds with general formula A were prepared by coupling 3-chloropyrazine-2-carbonitrile (1) with 4-hydroxymethyl benzene boronic acid, converting the resulting benzyl alcohol (2) to the benzyl chloride (3) with thionyl chloride and reacting this with a range of nucleophiles (R^1-# from List 1 and List 2; # = H) to give (4) (R^1-# from List 1 and List 2; # = point of attachment). The carbonitriles were then hydrolysed to give the acids (A).



(Scheme1)

Methods of Synthesising Compounds of Formula B (Scheme 2)

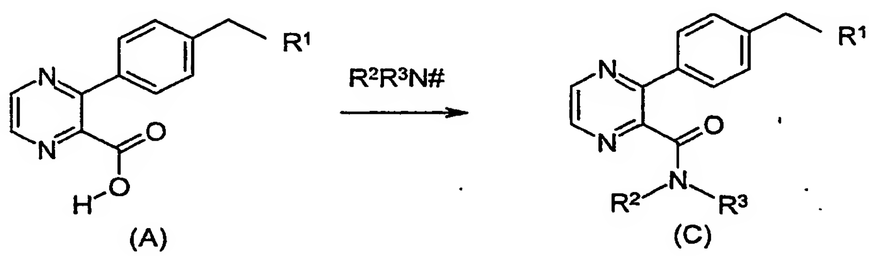
The carbonitriles (4) were converted to the tetrazoles (B) with trimethylsilyl azide, R^1 as above.



(Scheme 2)

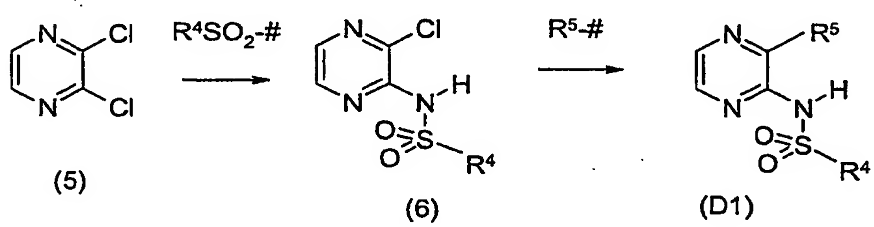
Methods of Synthesising Compounds of Formula C (Scheme 3)

Acids (A) were reacted with oxalyl chloride to give the corresponding acid chlorides and these were reacted with amines (R^2R^3N-# from List 3; # = H) to give the amides (C) (R^2R^3N-# from List 3; # = point of attachment)



(Scheme 3)

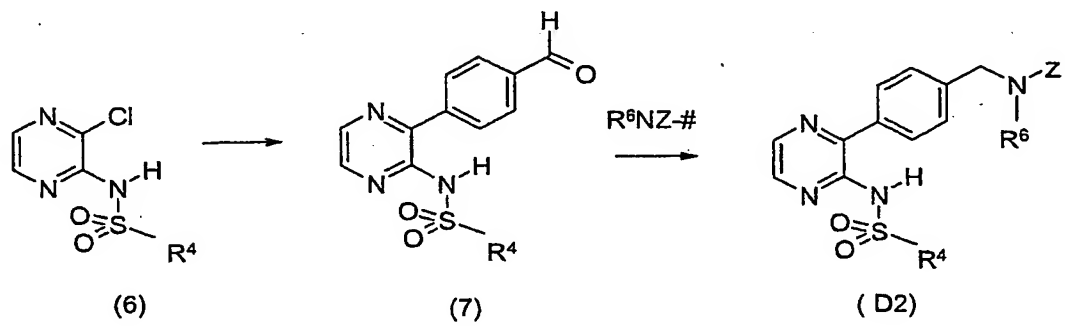
Methods of Synthesising Compounds of Formula D1 (Scheme 4a)



(Scheme 4a)

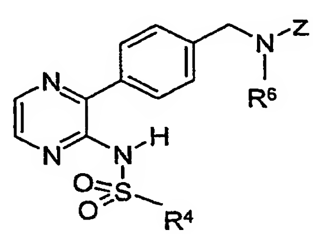
2,3-dichloropyrazine (5) was reacted with sulphonic acid amides (R^4SO_2NH-# from List 5; # = H) to give a range of sulphonic acid (3-chloropyrazin-2-yl) amides (6), these were coupled with a range of aromatic or heteroaromatic boronic acids (R^5-# from List 7; # = $B(OH)_2$) to give sulphonic acid amides (D1) (R^4SO_2NH-# from List 5; # = point of attachment: R^5-# from List 7; # = point of attachment).

Methods of Synthesising Compounds of Formula D2 (Scheme 4b)



(Scheme 4b)

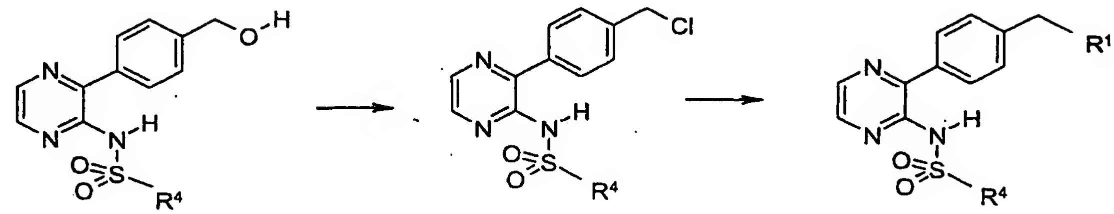
Aldehydes (7) were prepared by coupling sulphonic acid (3-chloropyrazin-2-yl) amides (6) with 4-formyl benzene boronic acid and these were converted to the benzylamines (D2) (R^6NZ-# from List 4; Z = H or Me; # = point of attachment) by reductive amination with amines (R^6NZ-# from List 4; # = H).



(D2a)

Compounds (D2), with Z = H, were reacted with acid chlorides and sulphonyl chlorides from List 6 where # = Cl in the presence of base to give amides and sulphonamides (D2a) (Z = acyl and sulphonyl groups from List 6 where # = point of attachment)

Methods of Synthesising Compounds of Formula D3 (Scheme 4c)

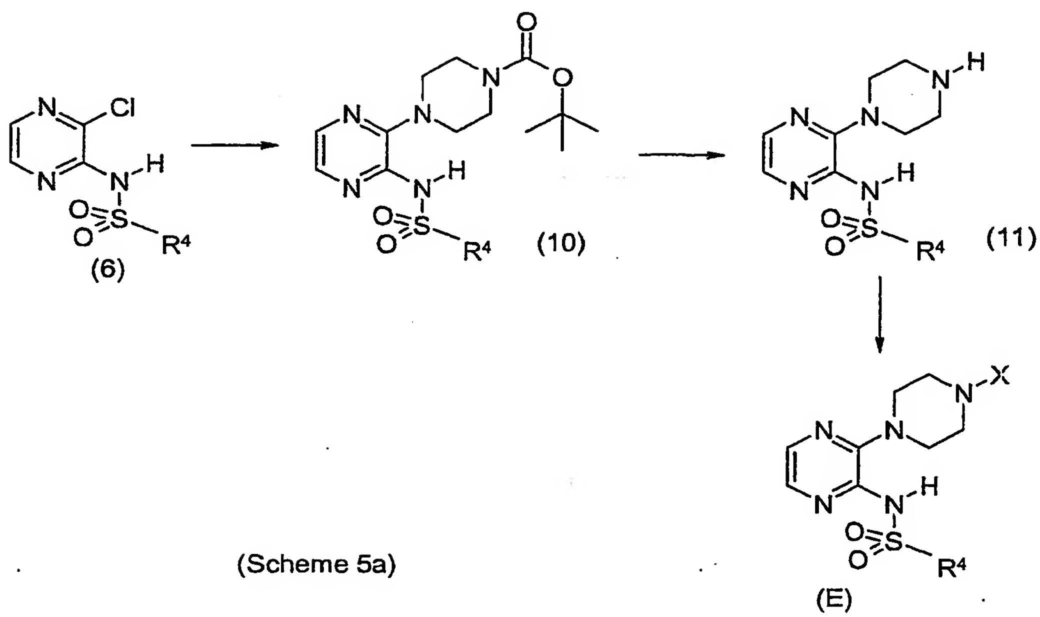


(8) (9) (D3)

(Scheme 4c)

Benzyl alcohols (8) were prepared by coupling the sulphonic acid (3-chloropyrazine-2-yl) amides (6) with 4-hydroxymethyl phenyl boronic acid and these were converted to the benzyl chlorides (9) with thionyl chloride. Reacting with a range of nucleophiles (R^1-# from List 1 and List 2; # = H) gave compounds (D3) (R^1-# from List 1 and List 2; # = point of attachment)

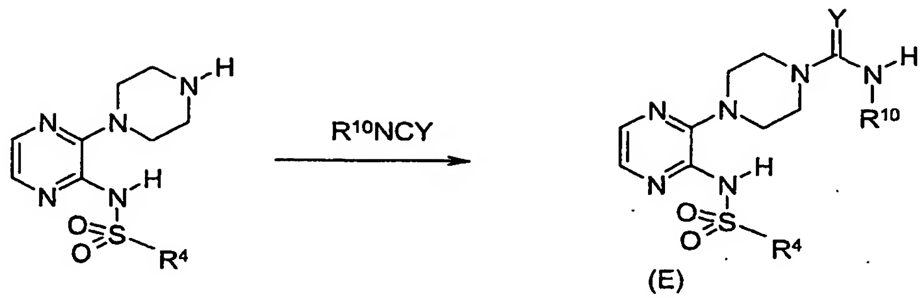
Methods of Synthesising Compounds of Formula E (Scheme 5a)



(Scheme 5a)

Sulphonic acid (3-chloroyrazines-2-yl) amides (6) were reacted with piperazine-1-carboxylic acid tert-butyl ester to give compounds (10). The tert-butyl group was removed by treatment with a suitable acid to give piperazines (11), which were treated with acid chlorides (R^7CO-# from List 8; # = Cl); sulphonyl chlorides (R^8SO_2-# from List 9; # = Cl) and alkyl halides (R^9-# from List 11; # = halogen) to give compounds of formula (E). X is either R^7CO-# from List 8, R^8SO_2-# from List 9 or R^9-# from List 11. In each case # is the point of attachment.

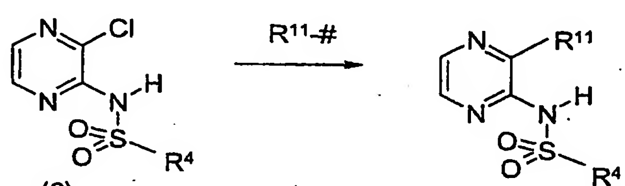
Methods of Synthesising Compounds of Formula E (Scheme 5b)



(11) (Scheme 5b) (E)

The piperazines (11) were reacted with isocyanates and isothiocyanates (R^{10}=N=Y where R^{10} is from List 10 and Y = oxygen or sulphur) to give ureas and thioureas (E) (R^{10}NHCY-# from List 10 where # is the point of attachment).

Methods of Synthesising Compounds of Formula E (Scheme 5c)

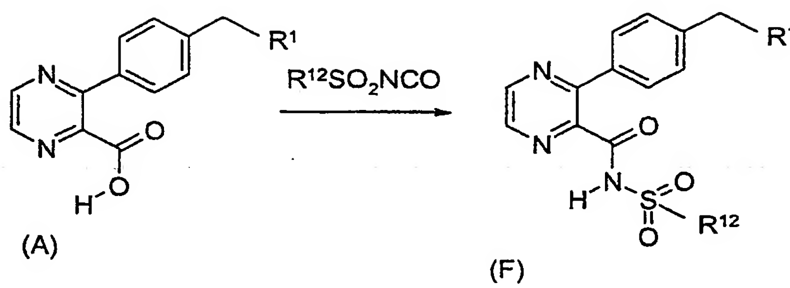


(6) (E)

(Scheme 5c)

1-heteroaryl or 1-aryl piperazines (R^{11}-# from List 12 where # = H) were heated with sulphonic acid (3-chloroyrazines-2-yl) amides (6) to give compounds (E) directly (R^{11}-# from List 12 where # = point of attachment).

Methods of Synthesising Compounds of Formula F (Scheme 6)



(Scheme 6)

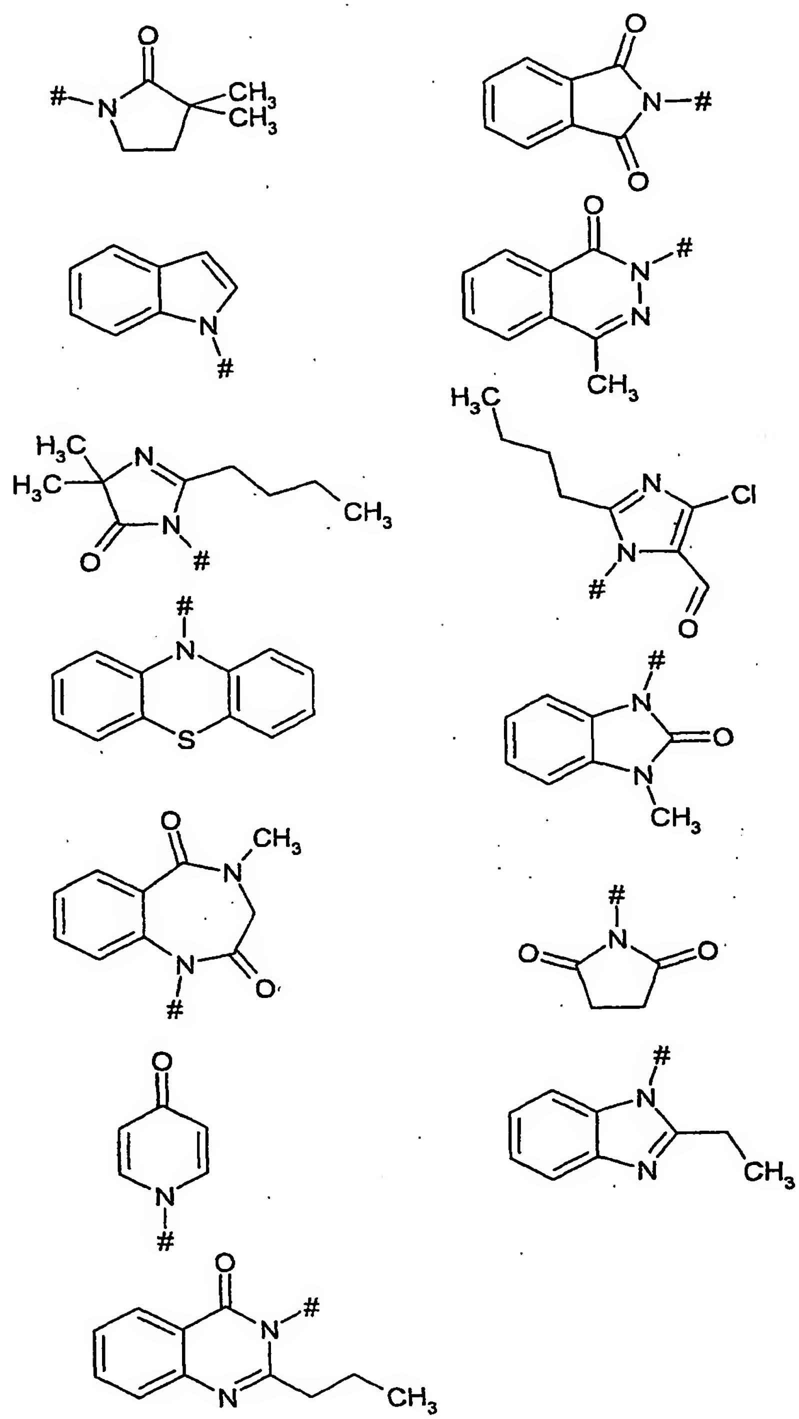
Acids (A) were reacted with sulphonyl isocyantes ($R^{12}SO_2NCO$ where R^{12} is from List 13) in the presence of base to give acyl sulphonamides (F) ($R^{12}SO_2NH$-# from List 13 where # = point of attachment).

Other methods for the synthesis of the intermediates will be apparent to the chemist skilled in the art as will be the methods for preparing starting materials and intermediates. The isolated novel compounds were confirmed by 1H N.M.R and/or other appropriate methods.

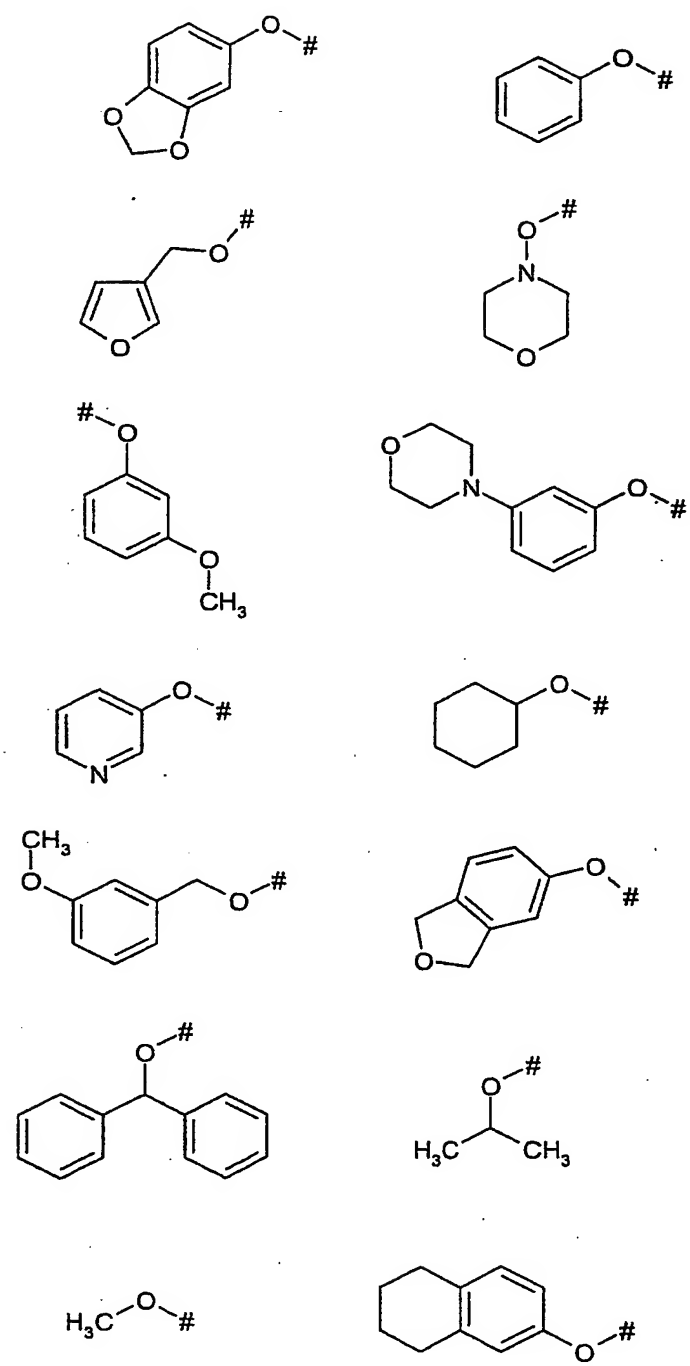
In the priority application (GB 0230195.0) where alternative groups are shown in place of #s, these groups may be modified to form leaving groups.

The permitted substituents at positions R1 to R12 for compounds of Libray 5 (SFG05) are shown below.

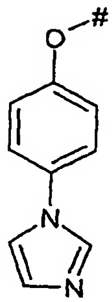
List 1 (R^1-#)

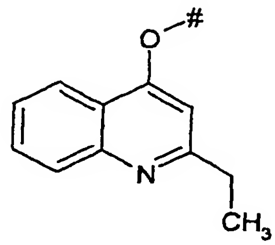


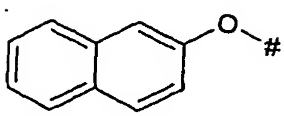
List 2 (R^1-#)

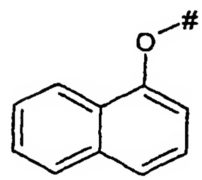


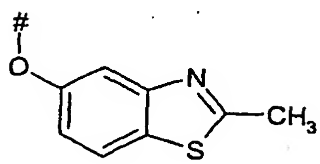
List 2 (Continued)

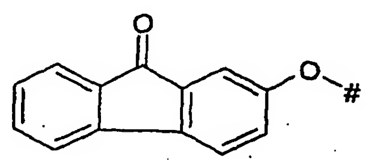


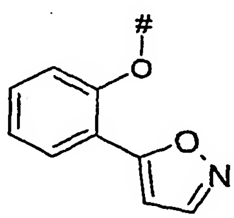




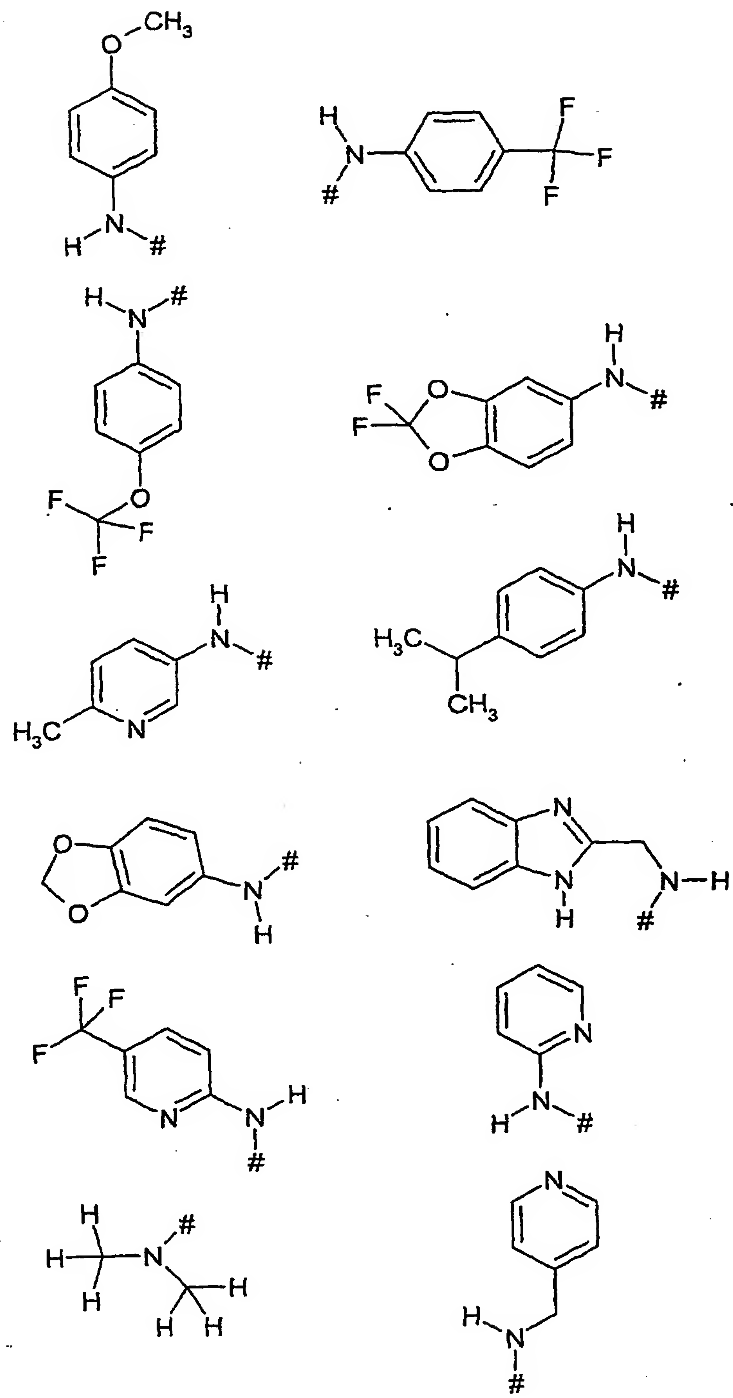








List 3 (R^2R^3N-#)



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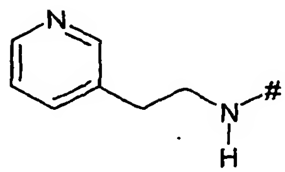
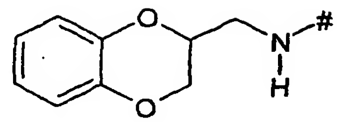
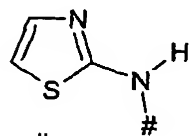
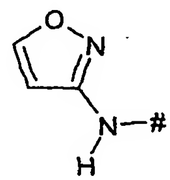
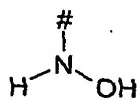
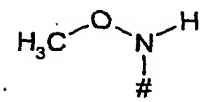
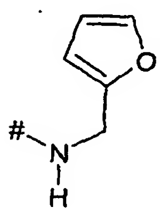
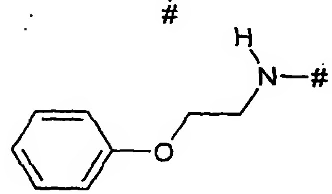
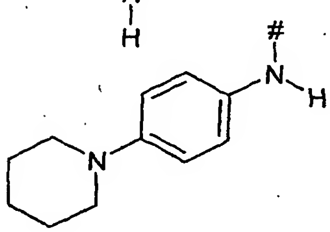
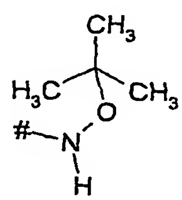
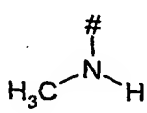
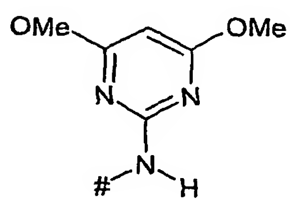
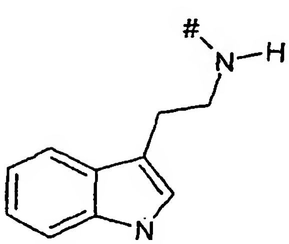
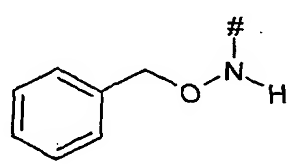

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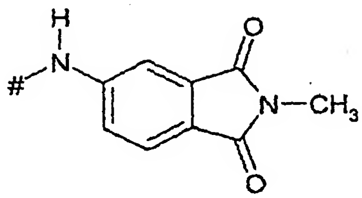
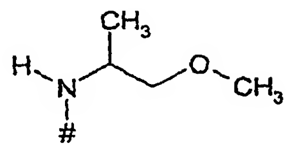
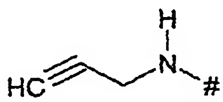
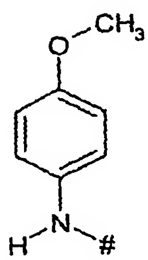
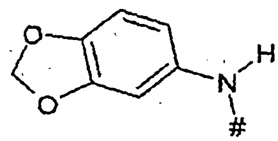


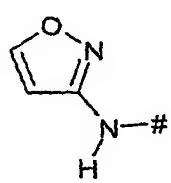


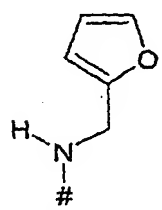


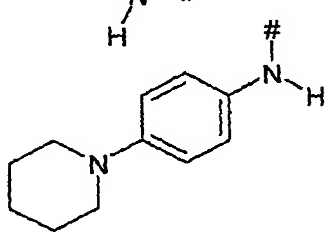
List 4 (R^6NZ-#)

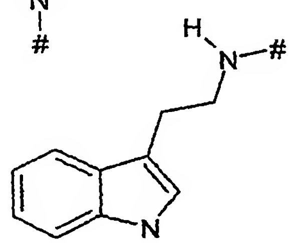


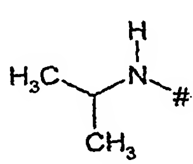


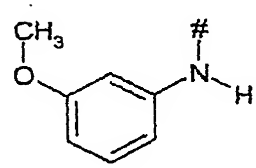












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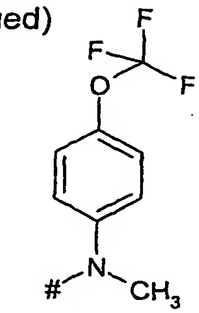
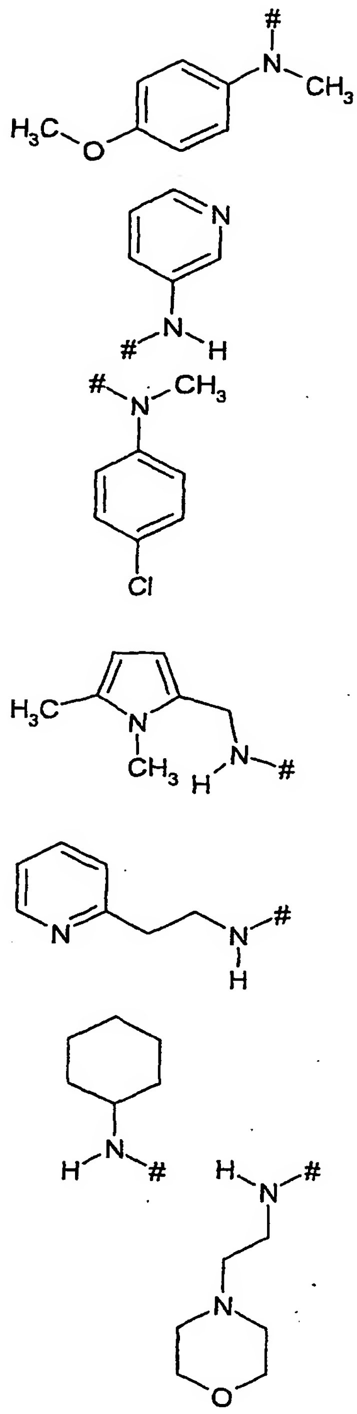
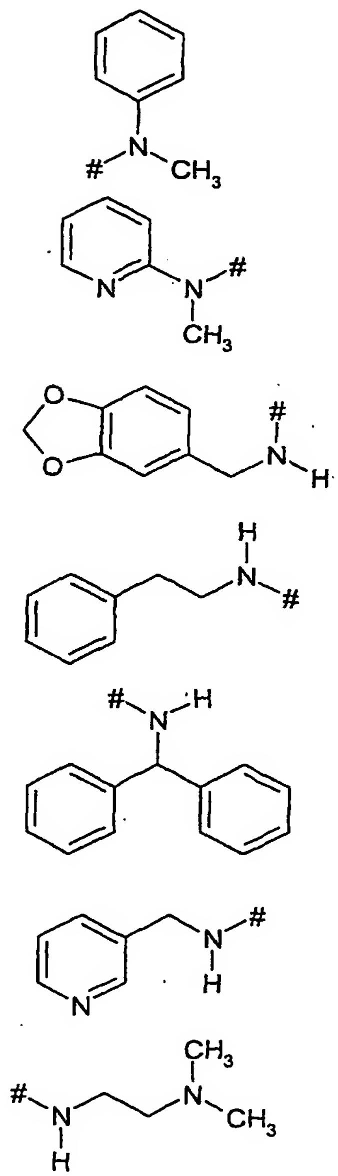
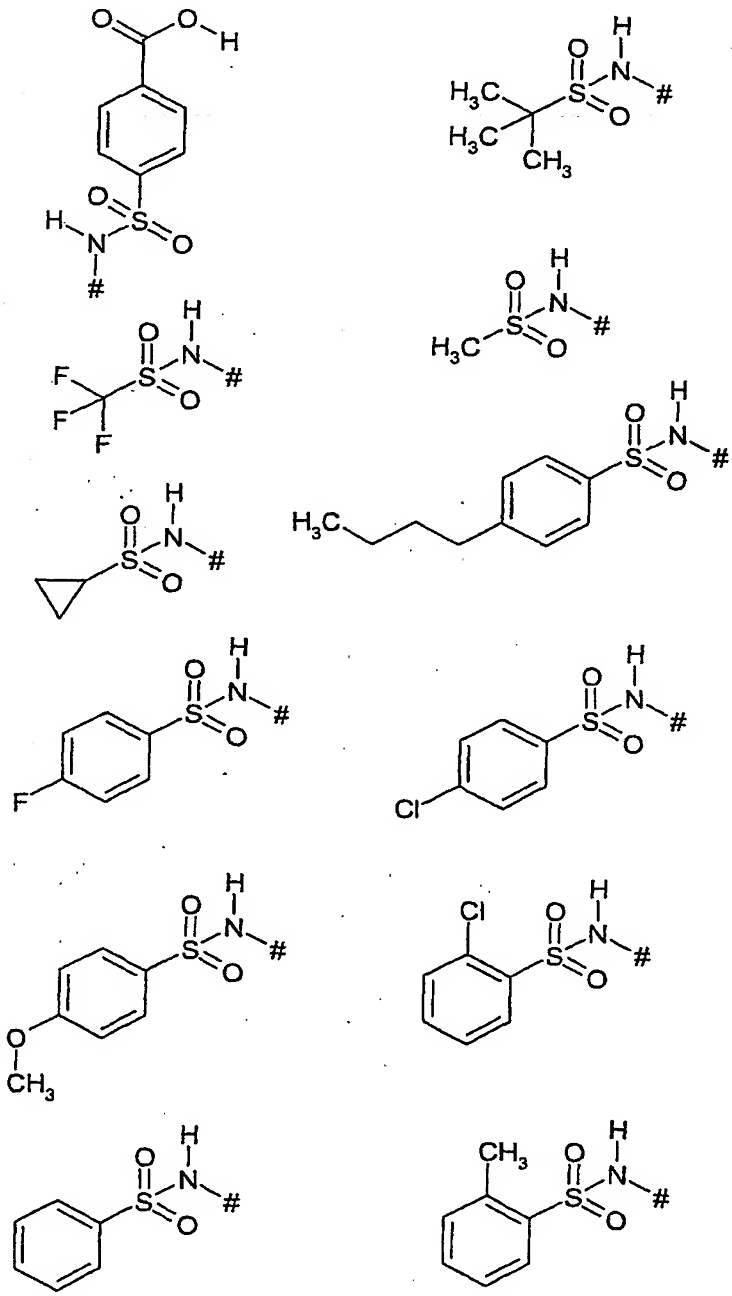






List 5 (R^4SO_2NH-#)



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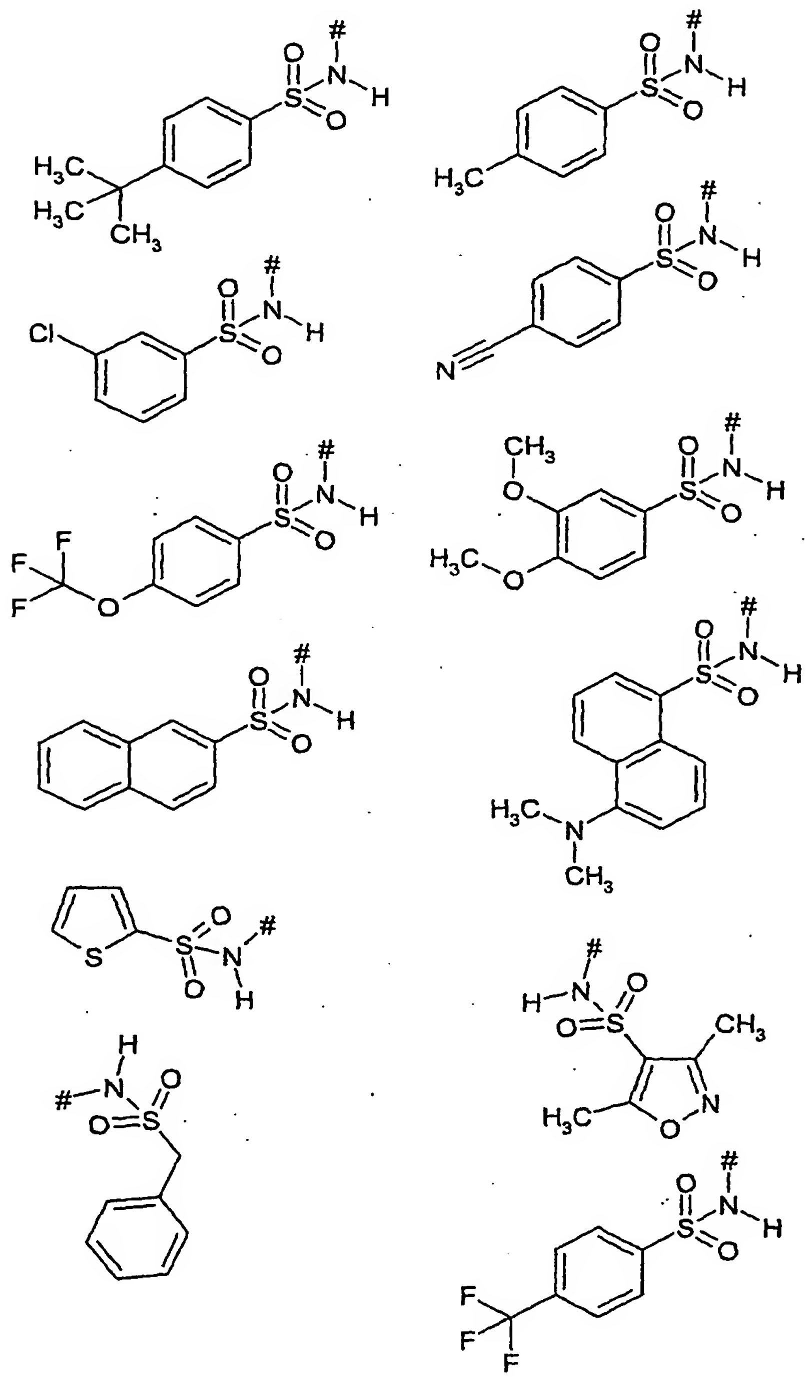

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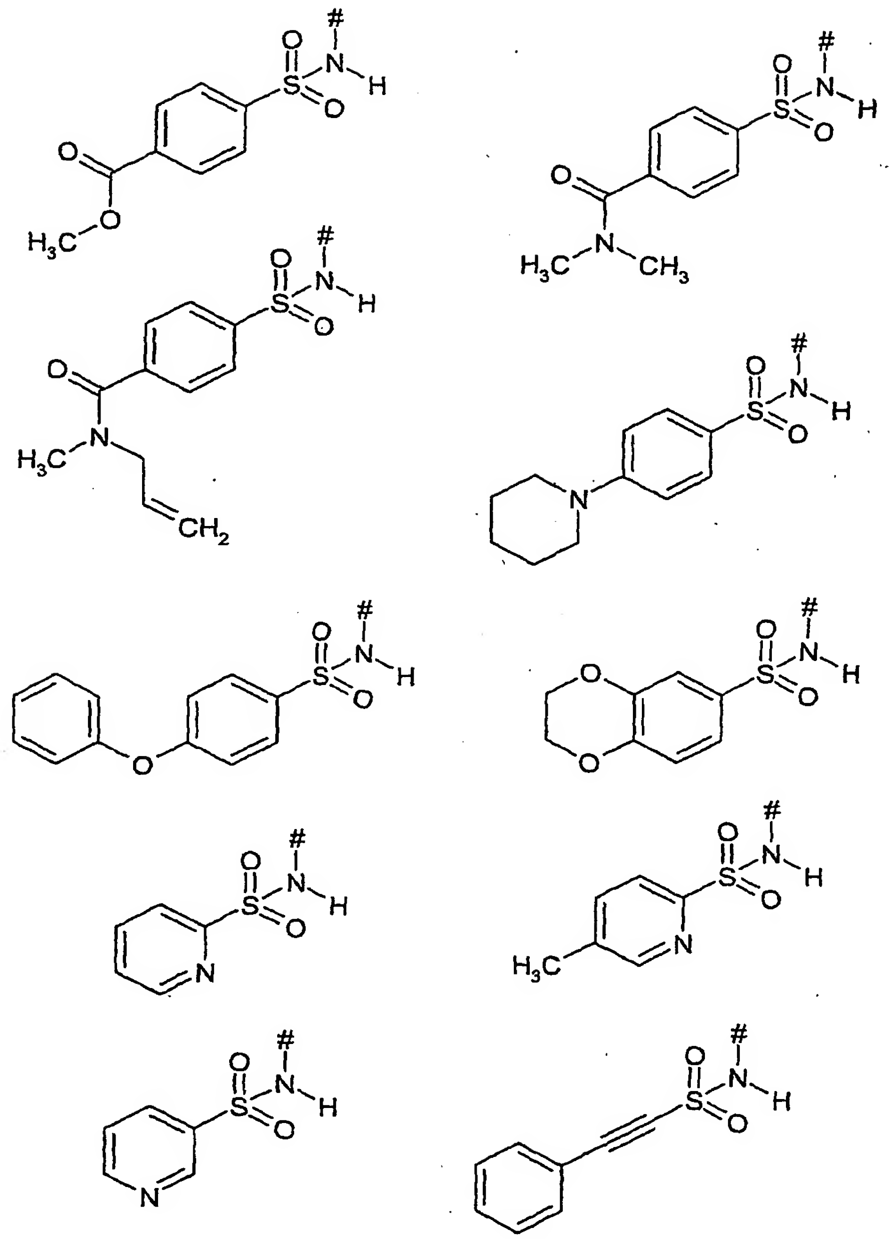

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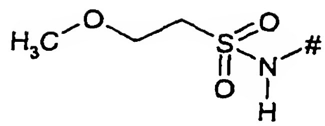

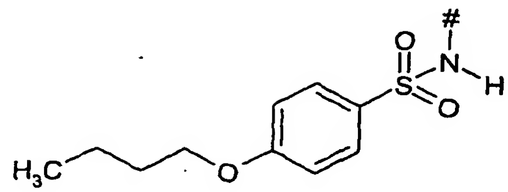

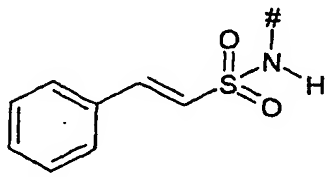

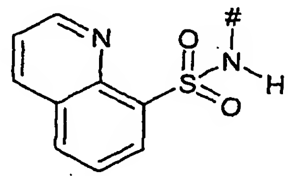

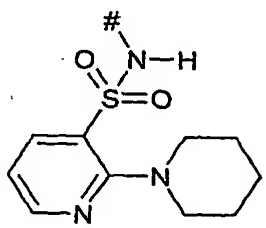

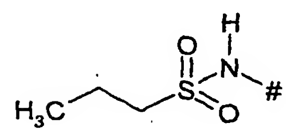

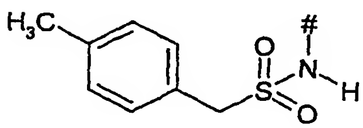

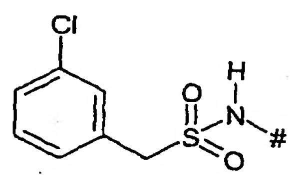

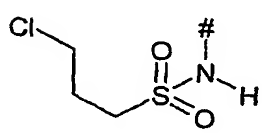

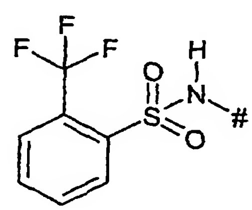

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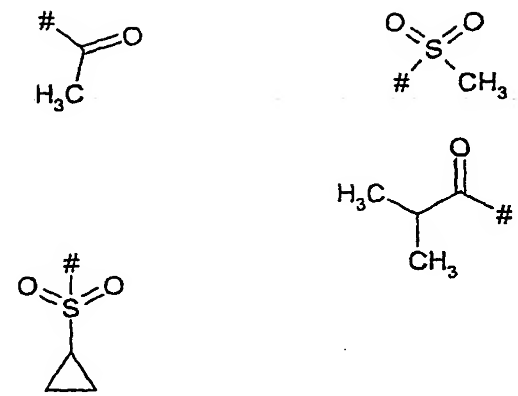

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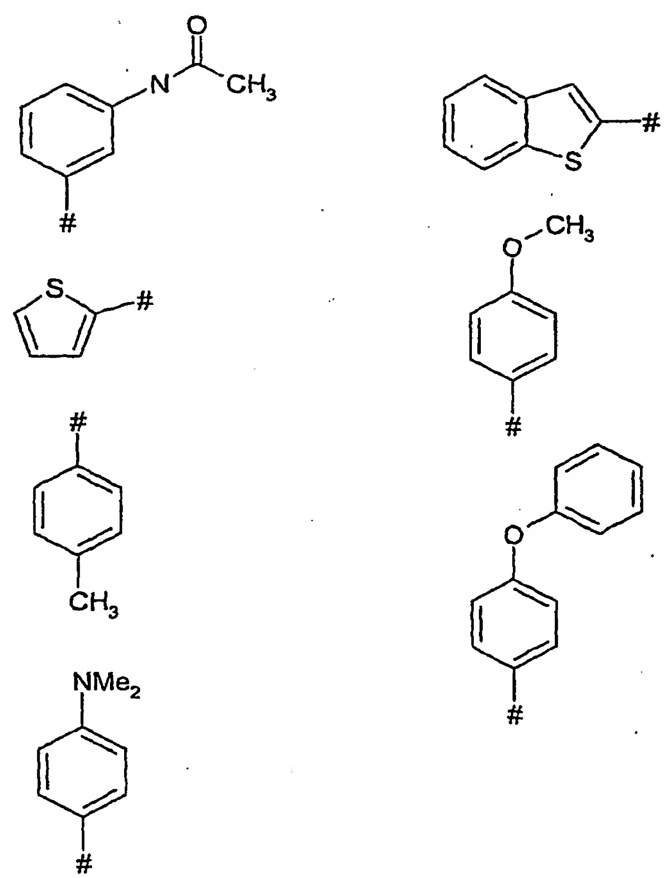

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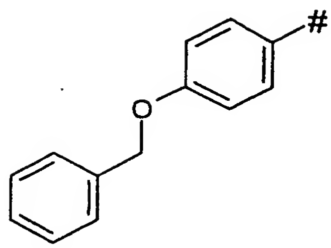
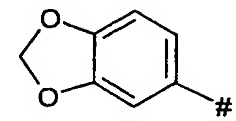
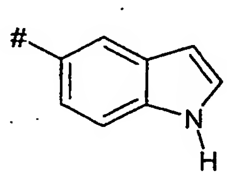
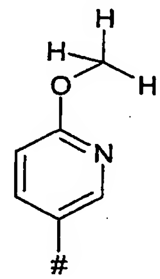
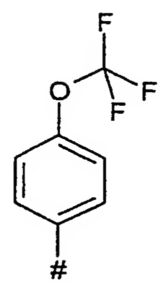
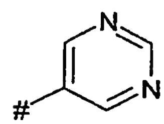


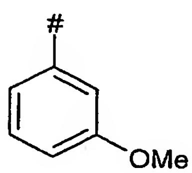


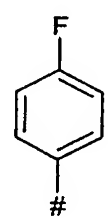


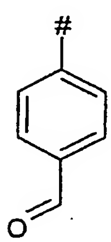


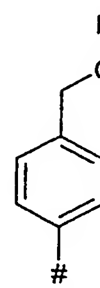




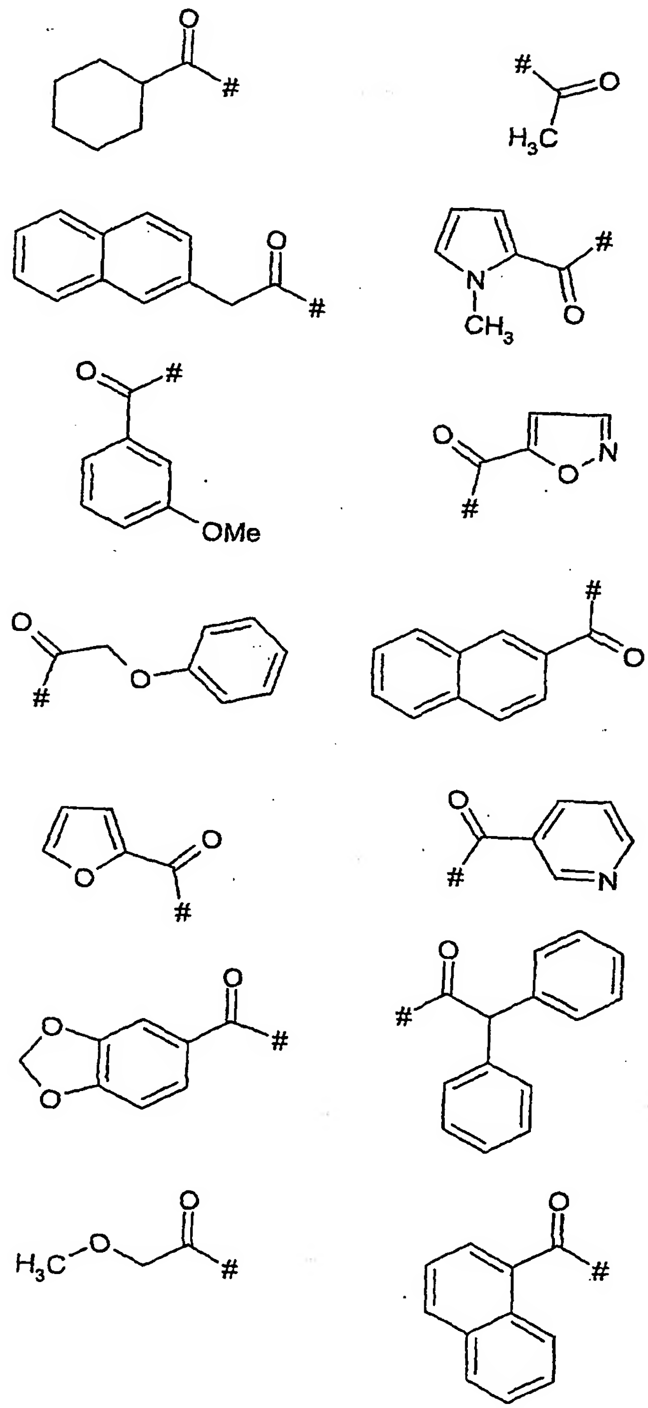








List 8 (R^7CO-#)



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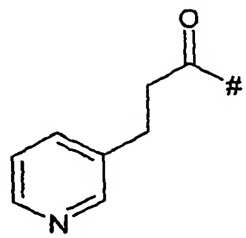

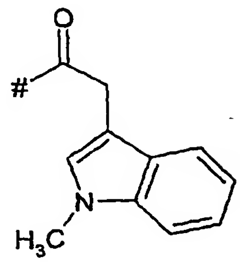

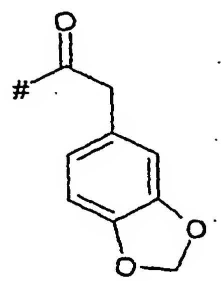

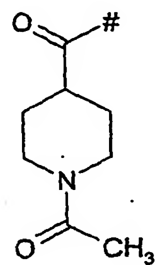

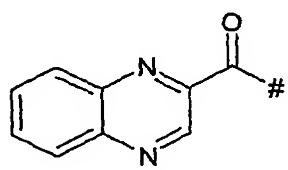

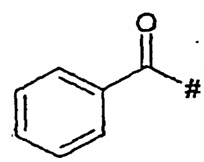

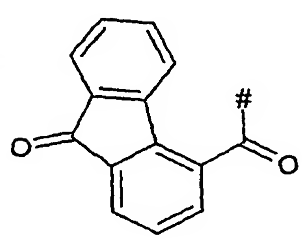

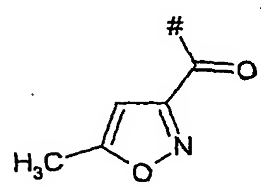

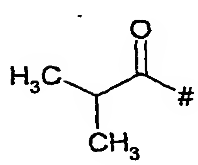

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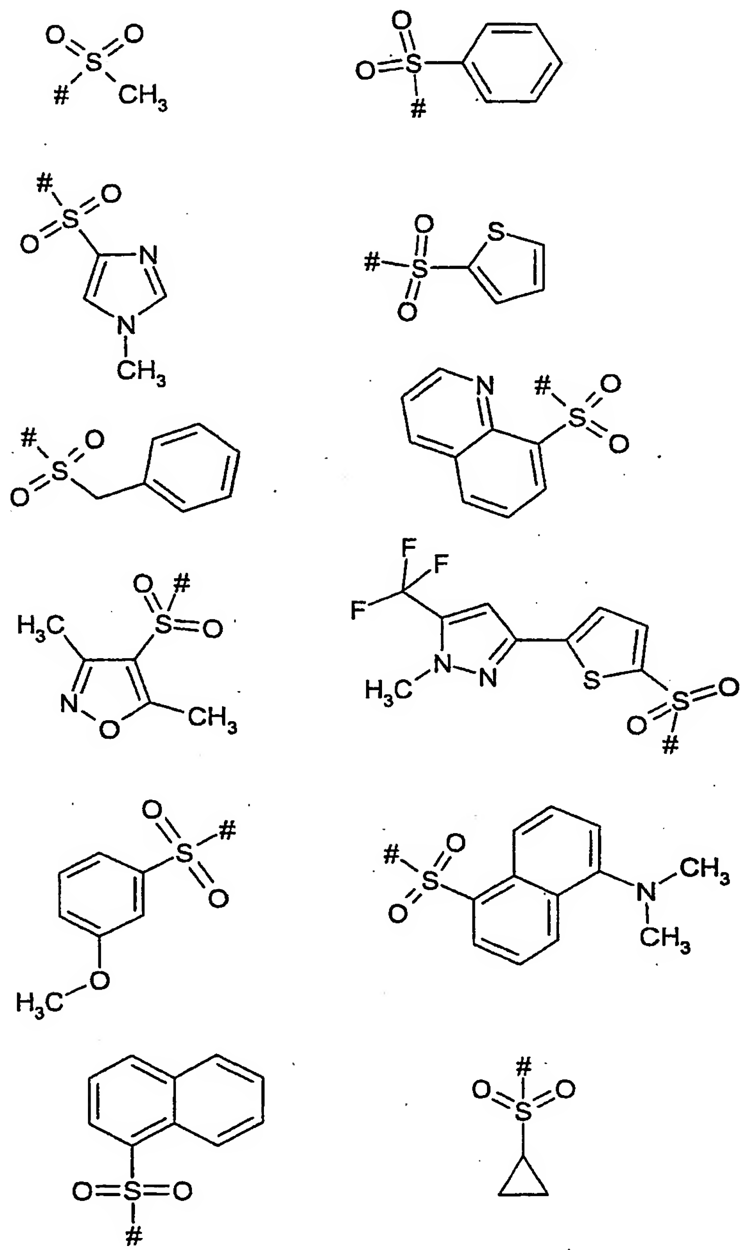
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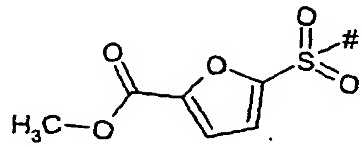
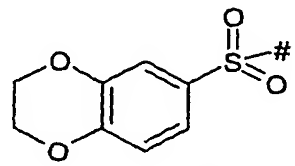
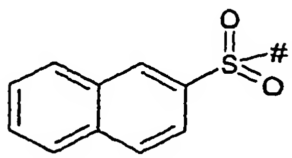
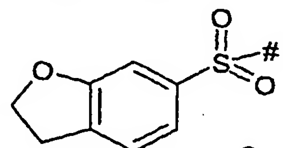
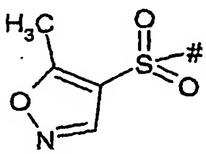
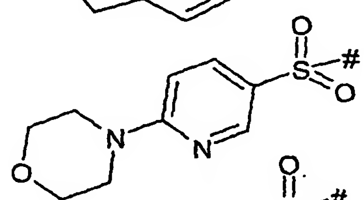
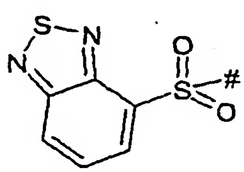
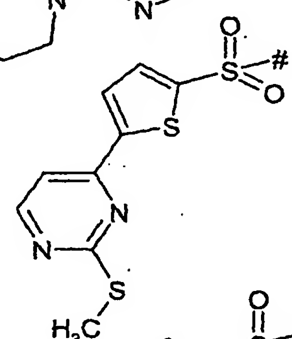
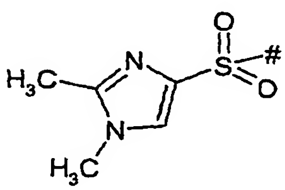
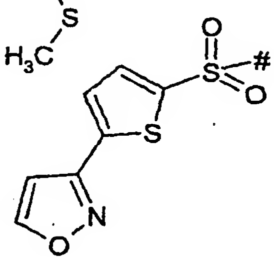
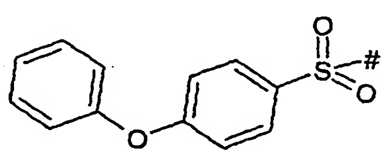
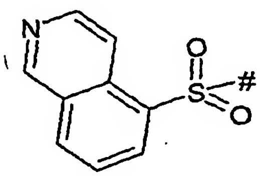
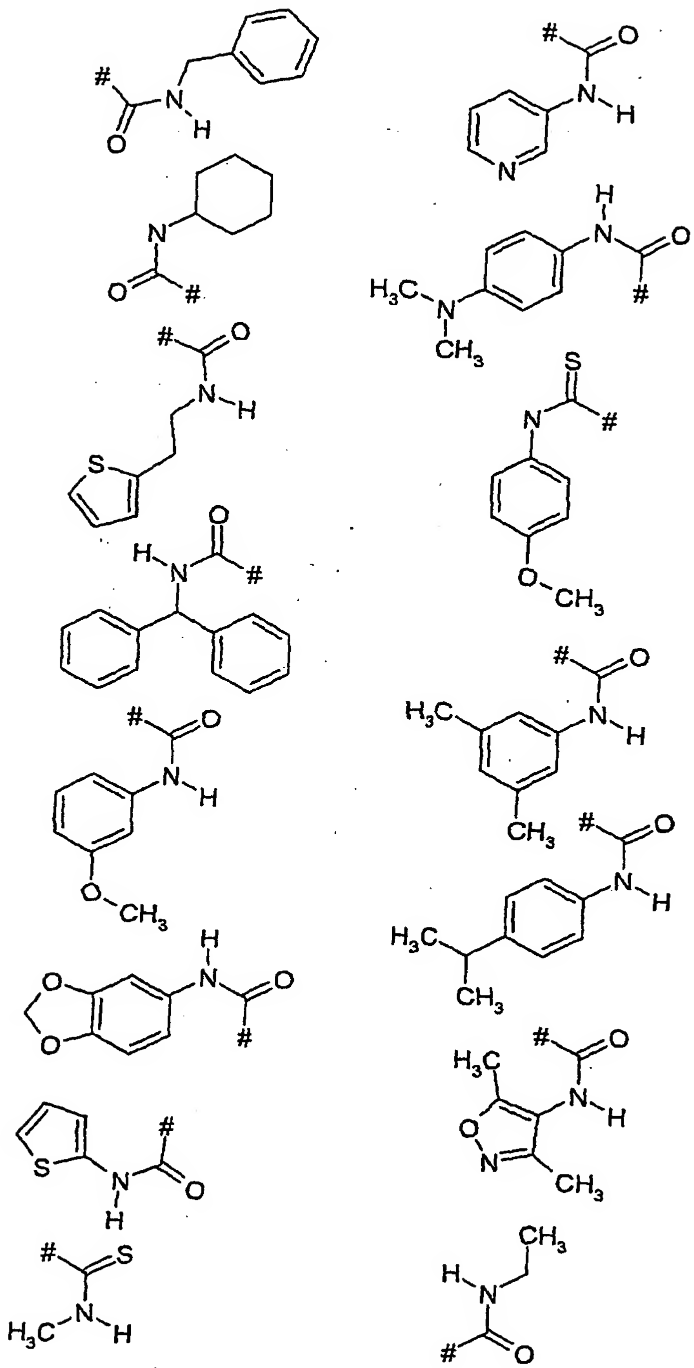
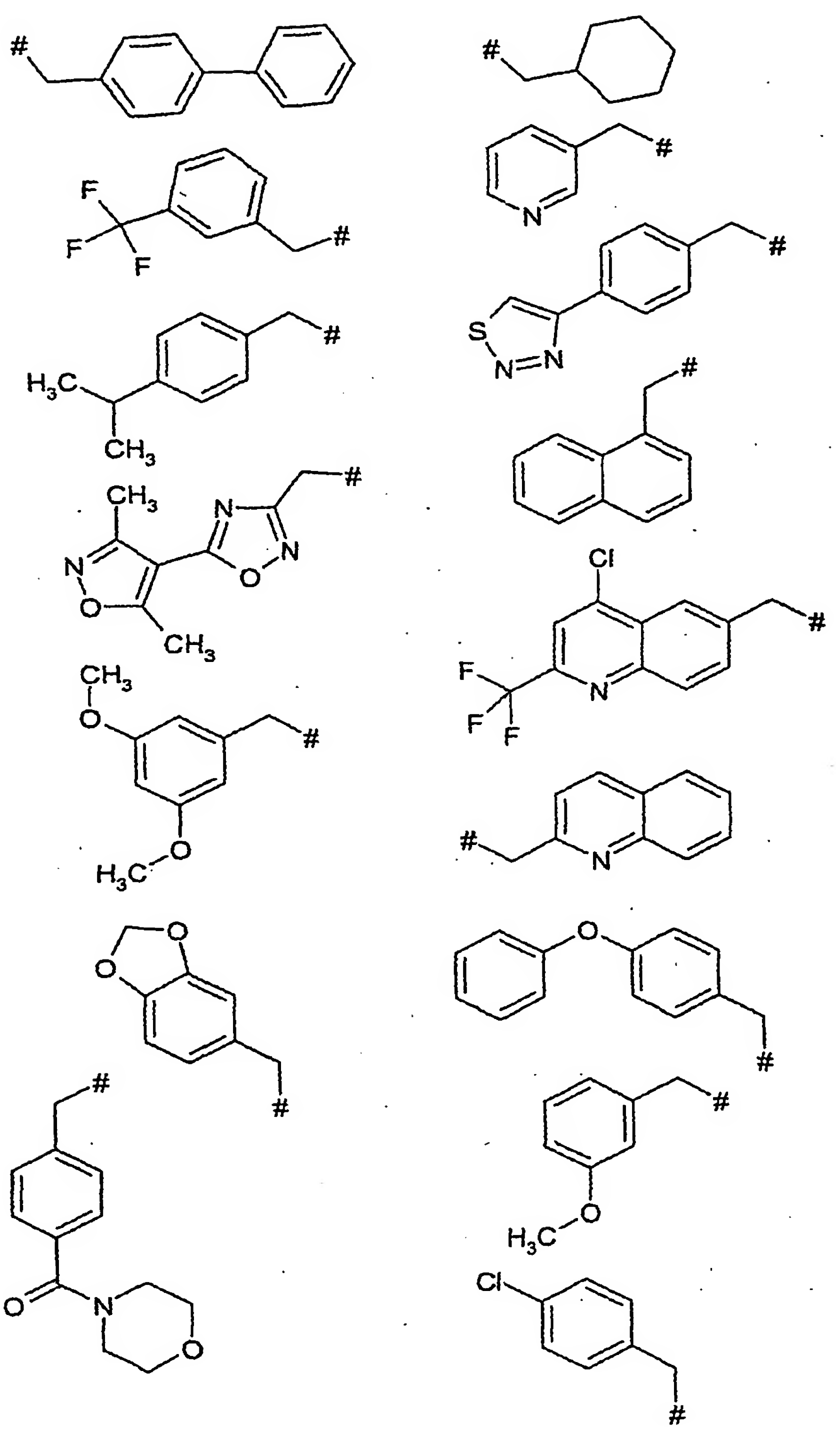













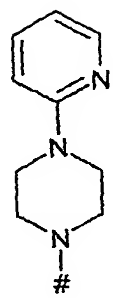
List 10 (R^{10}NHCO-#)

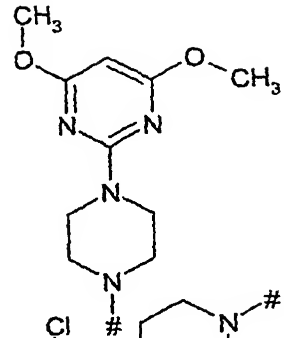


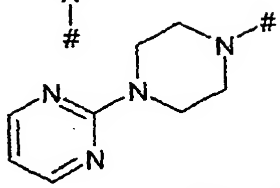
List 11 (R^9-#)

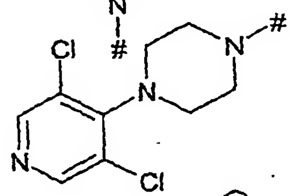


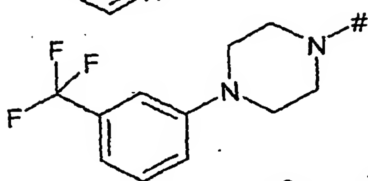
List 12 (R^{11}-#)

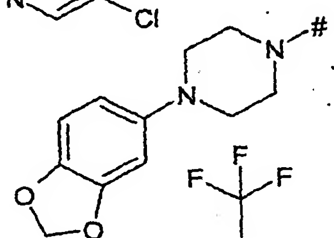


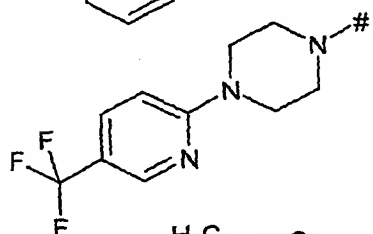


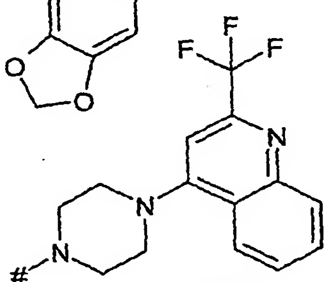


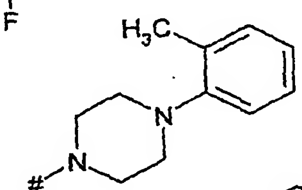


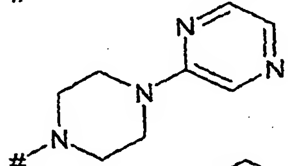


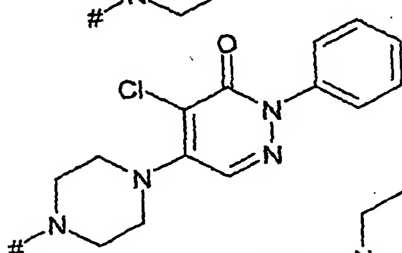


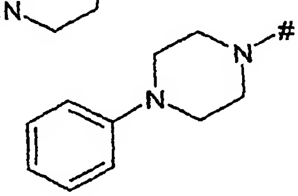


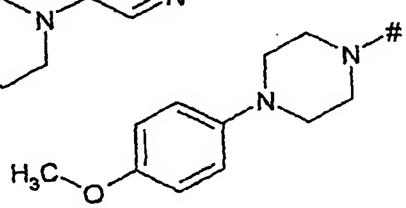




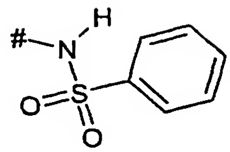


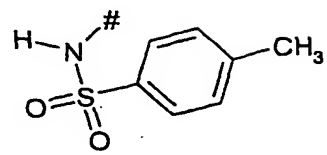


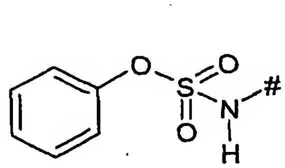


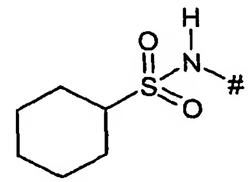


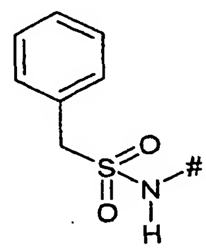
List 13 ($R^{12}SO_2NH$-#)

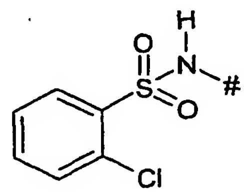


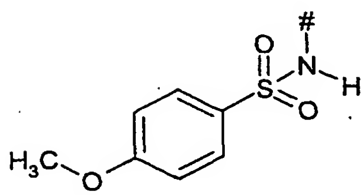


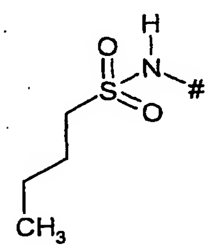


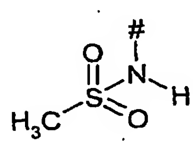


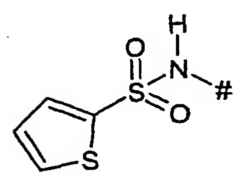








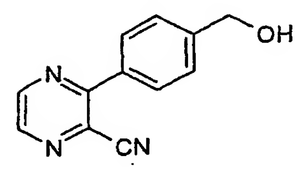




Examples

Example of synthesis of compound with General Formula A

3-(4-hydroxymethyl phenyl) pyrazine-2-carbonitrile (example of 2)

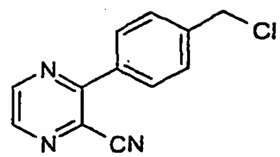


3-chloroprazine-2-carbonitrile (1.39g (0.01 mol)) and 4-hydroxymethyl phenyl boronic acid (1.5g, 0.011 mol) were dissolved in dimethoxyethane (30ml) and potassium carbonate (3.8g) in water (15ml) added. Triphenyl phosphine (0.39g) and Palladium (II) acetate (0.11g) were added and the mixture was stirred and heated to 90°C overnight, after cooling the reaction was diluted with ethyl acetate (30ml), filtered through celite and the organic layer separated, dried and evaporated. Purified by flash chromatography eluting with 1:1 ether/petrol to give 1.4g of 3-(4-hydroxymethyl phenyl) pyrazine-2-carbonitrile 3-(4-hydroxymethyl phenyl) pyrazine-2-carbonitrile as a cream solid.

δ_H(400 MHz; $CDCl_3$)

4.8 (d) 2H; 7.6 (d) 2H; 8.0 (d) 2H; 8.6 (s) 1H; 8.85 (s) 1H

3-(4-chloromethyl phenyl)-pyrazine-2-carbonitrile (example of 3)

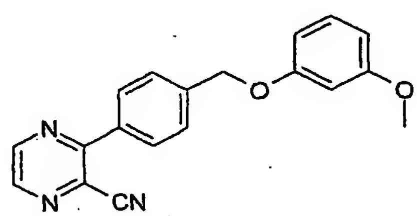


3-(4-hydroxymethyl phenyl) pyrazine-2-carbonitrile (0.5g, 0.005 mol) was dissolved in dichloromethane (10ml) and thionyl chloride (0.73ml) added dropwise. Stirred overnight at room temperature and then poured into ice/water (20ml). The organic layer was separated, dried and evaporated. The crude product was purified by flash chromatography eluting with ethyl acetate/petrol ether 1:2 to give 0.85g of 3-(4-chloromethyl phenyl)-pyrazine-2-carbonitrile as a cream solid.

δ_H(400 MHz; $CDCl_3$)

4.65 (s) 2H; 7.6 (d) 2H; δ8.0 (d) 2H 8.7 (s) 1H; 8.9 (s) 1H

3-[4-(3-methoxy phenoxymethyl)phenyl]pyrazine-2-carbonitrile (example of 4)

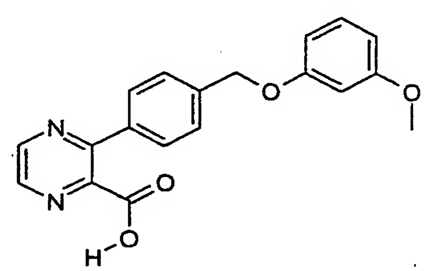


3-methoxy phenol (0.43g, 0.0035 mol) in dimethyl formamide (10ml) was treated with sodium hydride (0.14g (60% dispersed in oil), 0.0035 mol). After the evolution of hydrogen ceased, 3-(4-chloromethyl phenyl)-pyrazine-2-carbonitrile (0.8g, 0.0035 mol) in dimethyl formamide (5ml) was added and the solution heated to 80°C over

3 hours. The reaction was cooled, diluted with 30ml water and extracted with ether. The organic layer was dried and evaporated. Flash chromatography, eluting with ethyl acetate/petrol ether 1:1, gave 0.65g of 3-[4-(3-methoxy phenoxymethyl)phenyl]pyrazine-2-carbonitrile as a pale yellow solid

δ_H(400 MHz; $CDCl_3$)
3.8 (s) 3H; 5.2 (s) 2H; 6.55 (m) 3H; 7.2 (m) 1H; 7.6 (d) 2H; 8.0 (d) 2H; 8.65 (s) 1H; 8.85 (s) 1H

3-[4-(3-methoxy phenoxymethyl)phenyl]pyrazine-2-carboxylic acid (example of A)



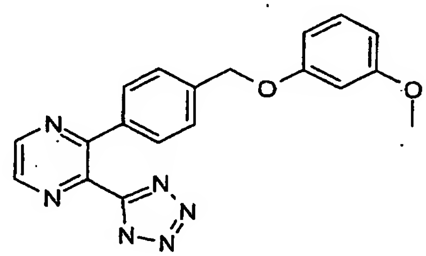
3-[4-(3-methoxy phenoxymethyl)phenyl]pyrazine-2-carbonitrile (1.11g, 0.0035 mol), 25ml of 4M aqueous sodium hydroxide solution and 15ml of methanol were heated to 85°C overnight to give a clear solution. This was cooled and the methanol evaporated. The aqueous solution was acidified with concentrated hydrochloric acid and extracted into ethyl acetate, washed with water dried and evaporated to give 1.2g of 3-[4-(3-methoxy phenoxymethyl)phenyl]pyrazine-2-carboxylic acid as a pale yellow glass.

δ_H(400 MHz; $CDCl_3$)

3.8 (s) 3H; 5.2 (s) 2H; 6.55 (m) 3H 7.2 (m) 1H; 7.5 (d) 2H; 7.6 (d) 2H; 8.6 (s) 1H; 8.9 (s) 1H

Example of synthesis of compound with General Formula B

2-[4-(3-methoxyphenoxymethyl)phenyl]-3-(1H-tetrazol-5-yl)pyrazine (example of B)



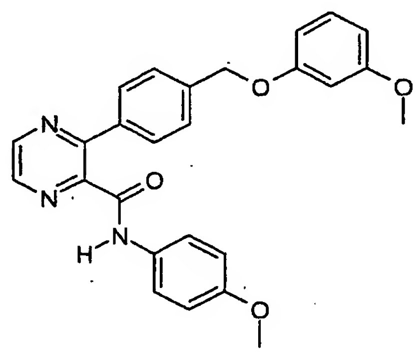
3-[4-(3-methoxy phenoxymethyl)phenyl]pyrazine-2-carbonitrile (0.127g, 0.4 mol), trimethylsilyl azide (0.11ml, 0.8 mol) and dibutyl tin oxide (20mg,0.08 mmol) in toluene (10ml) was heated at 100°C for 72 hours. The mixture was cooled and evaporated, the residue was dissolved in methanol and evaporated. The residue was then partitioned between ethyl acetate (5ml) and aqueous sodium bicarbonate (5ml). The two phases were separated and the organic layer extracted with a further 5ml aqueous sodium bicarbonate. The aqueous extracts were acidified with concentrated hydrochloric acid and extracted with ethyl acetate, dried and evaporated to give 0.12g of 2-[4-(3-methoxyphenoxymethyl)phenyl]-3-(1H-tetrazol-5-yl)pyrazine as a pink solid.

δ_H(400 MHz; $CDCl_3$)

3.8 (s) 3H; 5.2 (s) 2H; 6.55 (m) 3H; 7.2 (m) 1H; 7.4 (d) 2H; 7.5 (d) 2H; 8.6 (s) 1H; 8.8 (s) 1H

Example of synthesis of compound with General Formula C

3-[4-(3-methoxy phenoxymethyl)phenyl]pyrazine-2-carboxylic acid(4-methoxy phenyl)amide (example of C)



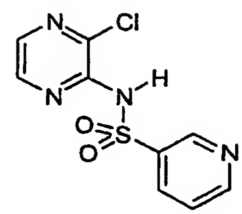
3-[4-(3-methoxy phenoxymethyl)phenyl]pyrazine-2-carboxylic acid (67mg, 0.22 mol) in dichloromethane (2ml) was treated with oxalyl chloride (0.1 ml of a 2M solution in dichloromethane (0.2 mmol)),stirred for 1.5 hours and added to a solution of 4-methoxy aniline (0.21 mol) in pyridine (0.7ml), shaken overnight at room temperature then evaporated. Treated with water, filtered and dried to give 3-[4-(3-methoxy phenoxymethyl)phenyl]pyrazine-2-carboxylic acid(4-methoxy phenyl)amide

LC/MS 82% pure Retention time 2.06min

M(-) 440

Examples of synthesis of compounds with General Formula D1 -D3

Pyridine-3-sulphonic acid (3-chloropyrazin-2-yl) amide (example of 6)



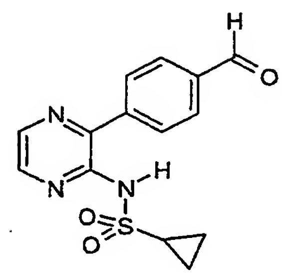
Pyridine-3-sulphonic acid amide (9.85g, 0.062 mol) and 2,3-dichloropyrazine (9.28g, 0.062 mol) were stirred in NMP (85ml), Cs_2CO_3 (22.36g, 0.069 mol) was added with stirring and the mixture was heated at 130°C overnight. The reaction was cooled, added to water (800ml) and washed with ethyl acetate (2x250ml). The aqueous phase was acidified with citric acid and extracted with ethyl acetate (3x500ml). The organic extracts were combined, washed with brine (100ml), dried over $MgSO_4$ and evaporated down.

The residue was purified by chromatography using 50-100% ethyl acetate in petrol (Rf = 0.24 in 75% ethyl acetate) to give 9.75g of Pyridine-3-sulphonic acid (3-chloropyrazin-2-yl)amide

δ_H(400 MHz; $CDCl_3$)

7.5 (m) 1H; 7.95 (br)1H; 8.05 (s)1H; 8.13 (s)1H; 8.45 (m)1H; 8.85 (m)1H; 9.35 (m)1H

Cyclopropane sulphonic acid [3-(4-formyl phenyl)-pyrazin-2-yl]-amide (example of D1)

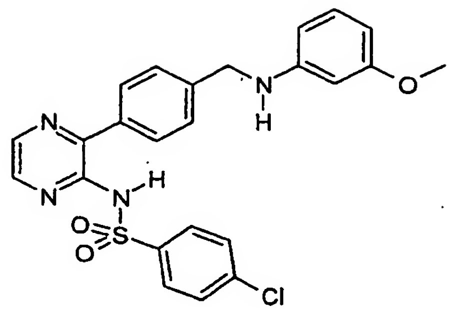


Cyclopropane sulphonic acid (3-chloro pyrazin-2-yl)amide (2.42g, 0.008mmol) and 4-formyl benzene boronic acid (1.4g, 0.0093 mol) were dissolved in dimethoxy ethane (30ml) and potassium carbonate (3.2g in 15ml water) added. Triphenyl phosphine (0.32g) and palladium (II) acetate (93mg) were added and the mixture stirred at 90°C overnight. The mixture was cooled and diluted with diethyl ether (60ml). Water (50ml) was added and the cloudy solution was filtered through celite. The aqueous layer was separated and washed with a further 25ml of ether. The aqueous solution was acidified with concentrated hydrochloric acid and extracted with ethyl acetate, the extracts were dried and evaporated to give a cream solid purified by flash chromatography eluting with dichloromethane/ethylacetate 9:1 to give 1.5g of Cyclopropane sulphonic acid [3-(4-formyl phenyl)pyrazin-2-yl]amide as a cream solid.

δ_H(400 MHz; $CDCl_3$)

1.15 (m) 2H; 1.4 (m) 2H; 3.3 (m) 1H; 7.2 (b) 1H; 7.9 (d) 2H; 8.0 (d) 2H; 8.35 (s) 1H; 8.4 (s) 1H; 10.1 (s) 1H

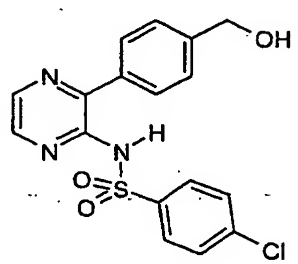
4-chloro-N-(3-(4-[(3-methoxy phenylamino)methyl]phenyl)pyrazin-2-yl)benzenesulphonamide (example of D2)



4-chloro-N-[3-(formyl phenyl)pyrazin-2-yl]benzene sulphonamide (75mg, 0.2 mmol) and 3-methoxy aniline (24.6mg, 0.2 mmol) were dissolved in dichloromethane (1ml). Acetic acid 0.1ml of a 2N solution in dichloromethane was added followed by sodium triacetoxy borohydride (68mg, 1.6 equivalent). The mixture was shaken overnight and the solution washed with water and evaporated to give 4-chloro-N-(3-(4-[(3-methoxy phenylamino)methyl]phenyl)pyrazin-2-yl)benzenesulphonamide as a brown gum.

LC/MS 90.6% pure M(-) 479 M(+) 481 Retention time 2.17 minutes

4-chloro-N-[3-(4-hydroxymethyl phenyl)pyrazin-2-yl]benzene sulphonamide (example of 8)



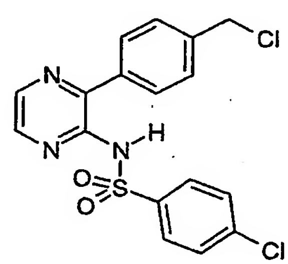
4-chloro-N-(3-chloro-pyrazin-2-yl)benzene sulphonamide 5.11g (0.0168 mol) and 4-hydroxymethyl benzene boronic acid 2.81g (0.0185 mol) were dissolved in dimethoxy

ethane 60ml and aqueous potassium carbonate (6.4g in 30ml water) added. Triphenyl phosphine (0.64g) and palladium (II) acetate (0.186g) were added and the mixture heated to 90°C and stirred overnight. Cooled, diluted with 100ml diethyl ether and 50ml water and filtered through celite. The aqueous layer was separated and the organic layer washed with 50ml water. The combined aqueous solutions were washed with 50ml diethyl ether then acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The extracts dried were over $MgSO_4$ and evaporated to give 4.9g of 4-chloro-N-[3-(4-hydroxymethyl phenyl)pyrazin-2-yl]benzene sulphonamide as a colourless solid.

δ_H(400 MHz; $CDCl_3$)

4.8 (s) 2H; 7.6-7.8 (m) 8H; 8.01-8.1 (m) 3H; 8.25 (s) 1H

4-chloro-N-[3-(4-chloromethyl phenyl)pyrazin-2-yl]benzene sulphonamide (example of 3)



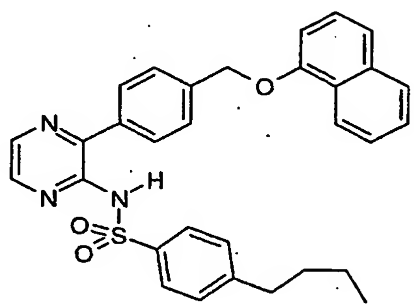
4-chloro-N-[3-(4-hydroxymethyl phenyl)pyrazin-2-yl]benzene sulphonamide (3.15g,0.084mol) was dissolved in dichloromethane (100ml) and thionyl chloride (8.4ml) added dropwise. The mixture was stirred overnight at room temperature. The solution was poured carefully into ice/water (200ml) and stirred until two clear layers were formed. The mixture was separated, the organic phase was dried and evaporated to give 2.45g of 4-chloro-N-[3-(4-

chloromethyl phenyl)pyrazin-2-yl]benzene sulphonamide as a cream solid.

δ_H(400 MHz; $CDCl_3$)

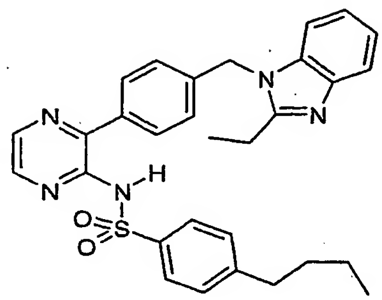
4.8 (s) 2H; 7.4 (s) 1H; 7.5 (d) 2H; 7.55 (dd) 4H; 8.05 (d) 2H; 8.1 (s) 1H; 8.3 (s) 1H

4-Butyl-N-{3-[4-(naphthalene-1-yloxymethyl)-phenyl]-pyrazin-2-yl}-benzenesulphonamide (example of D3)



4-butyl-N-[3-(4-chloromethyl phenyl)pyrazin-2-yl]benzene sulphonamide (83.3mg, 0.2mmol) was shaken in tetrahydrofuran (2ml) and 1-naphthol (32mg, 0.22mmol) in 0.5ml tetrahydrofuran was added followed by potassium-t-butoxide (0.9ml of an 0.5M solution in tetrahydrofuran). Shaken at 50°C overnight then cooled to room temperature, treated with 1ml of an aqueous citric acid solution (20g in 100ml water) and extracted into ethyl acetate. The organic layer was separated and evaporated. The residue was purified by preparative reverse phase HPLC to give 35.1mg of 4-Butyl-N-{3-[4-(naphthalene-1-yloxymethyl)-phenyl]-pyrazin-2-yl}-benzenesulphonamide (94% pure by LC/MS).

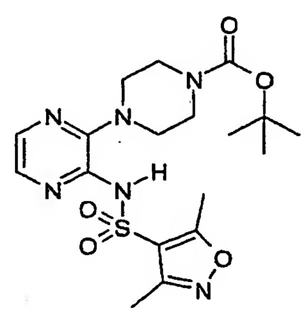
4-butyl-N-{3-[4-(2-ethyl benzoimidazol-1-yl)phenyl]pyrazin-2-yl}benzene sulphonamide (example of D3)



Prepared by the same method as 4-Butyl-N-{3-[4-(naphthalene-1-yloxymethyl)-phenyl]-pyrazin-2-yl}-benzenesulphonamide from 2-ethyl benzimidazole to give 34.4mg of 4-butyl-N-{3-[4-(2-ethyl benzoimidazol-1-yl)phenyl]pyrazin-2-yl}benzene sulphonamide (100% pure by LC/MS).

Example of synthesis of compound with General Formula E

3'-(3,5-dimethyl isoxazole-4-sulphonyl amino)-2,3,5,6-tetrahydro[1,2']bipyrazinyl-4-carboxylic acid *tert* butyl ester (example of 10)



3,5-dimethyl isoxazole-4-sulphonic acid (3-chloropyrazine-2-yl)amide (2.60g), 9 mmol) was stirred in N-methylpyrrolidone (5ml), piperazine-1-carboxylic acid tert-butyl ester(1.86g, 10 mmol) in N-methyl pyrrolidone

(I5ml) was added followed by Hunigs Base (1.83ml, 10.5 mmol), the mixture was heated at 140°C for 7½ hours and cooled.

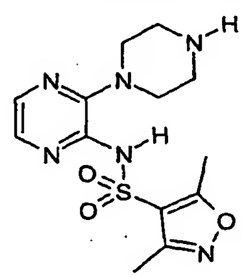
The reaction was added to water (200ml), acidified with AcOH (3ml) and extracted with ethyl acetate (4x50ml). The organic phases were combined, washed with water (2x100ml), dried over magnesium sulphate and evaporated down.

The residue was purified by flash chromatography using 40-60% ethyl acetate in petrol to give 2.83g of 3'-(3,5-dimethyl isoxazole-4-sulphonyl amino)-2,3,5,6-tetrahydro [1,2']bipyrazinyl-4-carboxylic acid *tert* butyl ester.

δ_H(400 MHz; $CDCl_3$)

1.45 (s) 9H; 2.45 (br) 3H; 2.6-2.8 (br d) 3H; 3.05 (br) 2H; 3.40-3.70 (br t) 6H; 6.85 (br) ½H; 7.40 (br) ½H; 7.55 (br) ½H; 7.85 (br) ½H; 7.95 (br) ½H; 12.05 (br) ½H

3,5-dimethyl isoxazole-4-sulphonic acid (3,4,5,6 tetrahydro-2H-[1,2']bipyrazinyl-3'-yl)amide trifluoroacetic acid salt (example of 11)



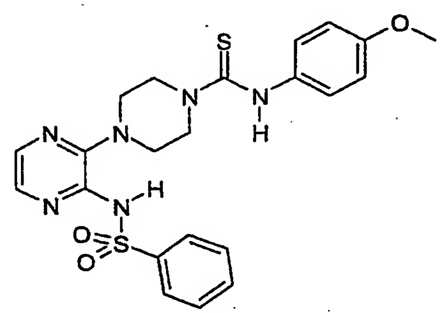
3'-(3,5-dimethylisoxazole-4-sulphonyl amino)-2,3,5,6-tetrahydro [1,2']bipyrazinyl-4-carboxylic acid tert butyl ester (2.82g, 6.44 mmol) was dissolved in dichloromethane (100ml), trifluoro acetic acid (6.4ml, 83.1 mmol) was added and the solution was allowed to stand over the week-end.

The reaction was evaporated under reduced pressure, azeotroped with methanol (50ml) toluene (50ml), dichloromethane (100ml) and diethyl ether (100ml) to give a quantitative yield of 3,5-dimethyl isoxazole-4-sulphonic acid (3,4,5,6 tetrahydro-2H-[1,2']bipyrazinyl-3'-yl)amide trifluoroacetic acid salt

δ_H(400 MHz;DMSO-d_6)

2.40 (s) 3H; 2.65 (s) 3H; 3.25 (br) 4H; 3.45 (br) 4H; 7.90 (br) 2H; 8.90 (br) 2H; 11.00 (br) 1H

3′-Benzenesulphonylamino-2,3,5,6-tetrahydro-[1,2′]bipyrazinyl-4-carbothioic acid (4-methoxy-phenyl)-amide (example of E)



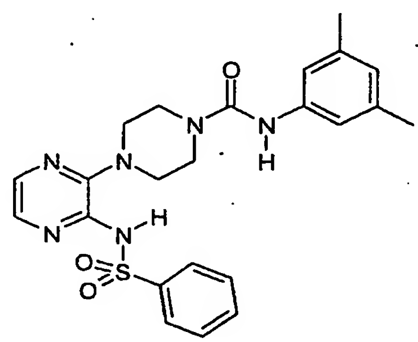
4-methoxy phenyl isothiocyanate (33mg, 0.2 mmol) in DMF (1ml) and 3′-benzenesulphonylamino-4-sulphonic acid (3,4,5,6 tetrahydro-2H-[1,2']bipyrazinyl-3'-yl)amide trifluoroacetic acid salt (0.2M in dimethyl formamide, 1ml, 0.2 mmol) and Hunigs Base (1M in DMF 1ml, 1.0 mmol) were allowed to stand for 2 hours, water (10ml) was added followed by 2% acetic acid in ethyl acetate(3ml), separated and extracted further with ethyl acetate (2x3ml). The organic phases were combined, washed with water (10ml), dried over magnesium sulphate and evaporated under reduced pressure. The residue was columned using 30-100% ethyl acetate in petrol to give 54mg of 3′-

Benzenesulphonylamino-2,3,5,6-tetrahydro-[1,2′]bipyrazinyl-4-carbothioic acid (4-methoxy-phenyl)-amide.

δ_H(400 MHz; $CDCl_3$)

3.55 (br) 4H; 3.80 (s) 3H; 3.95 (m) 4H; 6.85 (d) 2H; 7.10 (d) 2H; 7.15 (br) 1H; 7.45-7.60 (m) 4H; 8.00 (br) 2H

3′Benzenesulphonylamino-2,3,5,6-tetrahydro-{1,2′]bipyrazinyl-4-carboxylic acid (3,5-dimethyl-phenyl)-amide (example of E)

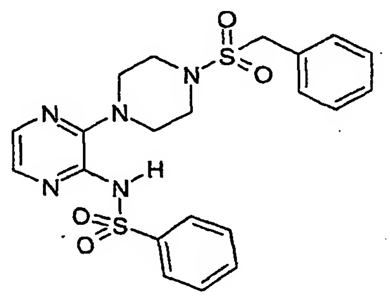


3,5-dimethyl phenyl isocyanate (31mg, 0.2 mmol), 3′-benzenesulphonylamino-4-sulphonic acid (3,4,5,6 tetrahydro-2H-[1,2']bipyrazinyl-3'-yl)amide trifluoroacetic acid salt (1ml, 0.2M in dimethyl formamide, 0.2 mmol) and Hunigs Base (1ml, 1.0M in dimethyl formamide, 1.0 mmol) were shaken overnight. The reaction was evaporated under reduced pressure, water (4ml) and 2% acetic acid in ethyl acetate (3.5ml) added, separated and extracted further with ethyl acetate (2x2ml). The combined organic phases were evaporated under reduced pressure and purified by reverse phase HPLC to give 58mg of 3′Benzenesulphonylamino-2,3,5,6-tetrahydro-{1,2′]bipyrazinyl-4-carboxylic acid (3,5-dimethyl-phenyl)-amide.

δ_H(400 MHz;DMSO-d_6)

2.25 (s) 6H;3.20-3.65 (br) 8H; 6.65 (s) 1H;7.20 (s) 2H; 7.70 (m) 3H; 8.0 (m) 2H; 8.45 (m) 1H

N-(4-Phenylmethanesulphonyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-yl)-benzenesulphonamide (example of E)

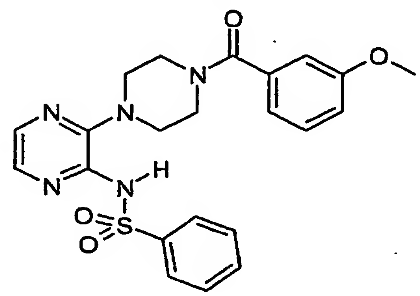


Benzyl sulphonyl chloride (38mg, 0.2 mmol) the 3'-benzenesulphonylamino-4-sulphonic acid (3,4,5,6 tetrahydro-2H-[1,2']bipyrazinyl-3'-yl)amide trifluoroacetic acid salt (1ml, 0.2M in dimethyl formamide, 0.2 mmol) and Hunigs Base (1ml, 1.0M in dimethyl formamide 1.0 mmol) were shaken overnight. The reaction was evaporated under reduced pressure, water (4ml) and 2% acetic acid in ethyl acetate (3.5ml) added, separated and extracted further with ethyl acetate (2x2ml). The combined organic phases were evaporated under reduced pressure and purified by reverse phase HPLC to give 39mg of N-(4-Phenylmethanesulphonyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-yl)-benzenesulphonamide.

δ_H(400 MHz;DMSO-d_6)

3.10-3.60 (br) 8H; 4.40 (s) 2H; 7.35 (m) 6H; 7.55 (m) 3H; 7.90 (m) 2H

N-[2-(3-methoxy-benzoyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-yl]-benzenesulphonamide (example of E)



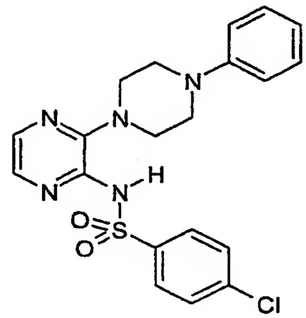
3-Methoxy benzoyl chloride (34mg, 0.2mmol), the 3'-benzenesulphonylamino-4-sulphonic acid (3,4,5,6 tetrahydro-2H-[1,2']bipyrazinyl-3'-yl)amide trifluoroacetic acid salt (1ml, 0.2M in DMF, 0.2 mmol) and Hunigs Base (1ml, 1.0M in DMF, 1.0mmol) were shaken overnight.

The reaction was evaporated, water (4ml) and 2% acetic acid in ethyl acetate (3.5ml) added, separated and extracted with ethyl acetate (2x2ml). The combined organic phases were evaporated under reduced pressure and purified by reverse phase HPLC to give 42mg of N-[2-(3-methoxy-benzoyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-yl]-benzenesulphonamide.

δ_H (400 MHz; DMSO-d_6)

3.20 (br) 8H; 3.55 (s) 3H; 6.75 (m) 3H; 7.10 (m) 1H; 7.35 (m) 3H; 7.70 (m) 2H

4-Chloro-N-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyazinyl-3'-yl)benzenesulphonamide (example of E)

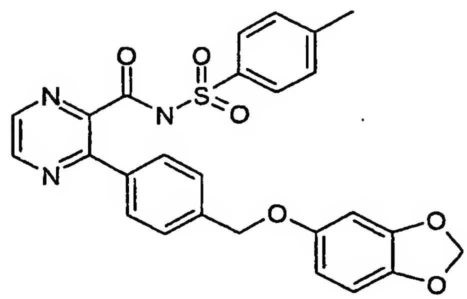


1-phenyl piperazine (170µl, 1.1mmol) was stirred in N-methylpyrrolidone (5ml), Hunigs Base (435µl, 2.5 mmol) was added followed by 4-Chloro-N-(3-chloro-pyrazin-2-yl)-benzenesulphonamide (305mg, 1.0mmol) and heated at 130°C for 22 hours. The reaction was cooled, water (25ml) added and basified with sodium hydroxide (4M, 2.5ml) and washed with ethyl acetate (75ml). The aqueous phase was acidified with acetic acid (1.25ml) and extracted with ethyl acetate (2x40ml). The organic phases were combined, washed with water (40ml), dried over magnesium sulphate and evaporated under reduced pressure. The product was purified by flash chromatography using 30% ethyl acetate in petrol to give 165mg of 4-Chloro-N-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyazinyl-3'-yl)benzenesulphonamide.

δ_H(400 MHz; $CDCl_3$)

3.20-3.40 (br t) 6H; 3.90 (br) 2H; 6.80-7.00 (br) 4H; 7.30 (br) 2H; 7.45-7.55 (br) 3H; 7.80-7.95 (br) 2H; 8.10 (br) 1H

N-{3-[4-(Benzo{1,3}dioxol-5-yloxymethyl)-phenyl]-pyrazine-2-carbonyl}-4-methyl-benzenesulphonamide (example of F)



3-[4-(Benzo[1'3]dioxol-5-yloxymethyl)-phenyl]-pyrazine-2-carboxyl acid (70mg) was dissolved in dry tetrahydrofuran (2.5ml) and a solution of triethylamine (0.2mmol) in dry tetrahydrofuran (0.5ml) was added. A solution of 4-Methyl-benzenesulphonyl isocyanate (0.2mmol) in dry tetrahydrofuran (0.8ml) was added and the reaction was shaken at room temperature overnight.

The reaction was concentrated under vacuum and treated with water (2ml) plus dichloromethane (3ml), the organic phase was separated and the aqueous phase extracted with a further 2ml of dichloromethane. The organic phases were combined and concentrated under vacuum. The residue was purified by reverse phase chromatography to give 24.3 mg of N-{3-[4-(Benzo{1,3}dioxol-5-yloxymethyl)-phenyl]-pyrazine-2-carbonyl}-4-methyl-benzenesulphonamide (97.3% pure by analytical HPLC)

Appendix 1

Analytical HPLC Conditions

Conditions	Detection
Column: Column Phenomenex LUNA C_{18}(2); 5µm; 30x4.6mm with 5mm guard. **Gradient:** (percent acetonitrile in water): 20-100 over 2.5 minutes then 100 for 1 minute followed by 20 for one minute. Formic acid was present at 0.1% throughout. **Flow rate:** 2 ml/min at 400-bar pressure. **Temperature:** 30 °C. **Injection volume:** 5 µL partial loop.	UV detection - diode array range 210-400 nm. **Electrospray ionisation:** Cone voltage: 30 V. Cone temperature: 20 °C. Source temperature 150 °C. RF lens voltage: 0.0 V. Ion energy: 0.5 eV. Multiplier: 650 V.

Preparative HPLC Conditions

All compounds were purified by reverse phase HPLC using a Gilson preparative HPLC system (321 pump, diode array detector, 215 liquid handler) and a Luna 10µm C_{18} 100 x 21mm column. A flow rate of 25 mL/min was used.

The Gilson 215 was used as both auto-sampler and fraction collector.

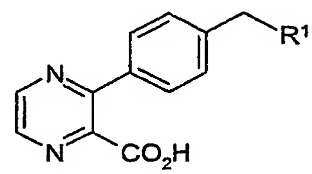
The gradient used was 95% water / 5% acetonitrile (each containing 0.1% formic acid) for 1.5 min to 95%

acetonitrile over 6 min then held at 95% acetonitrile for 3.0 min. The solvent mixture was then returned to the initial conditions over 0.25 min. The column was re-equilibrated over 2.5 minutes prior to the next injection.

The purification was controlled by Unipoint software, triggering a threshold collection value monitoring at 240 nm. Collected fractions were analysed by LCMS. The fractions that contained the desired product were concentrated by vacuum centrifugation and the resultant residue dried by freeze-drying.

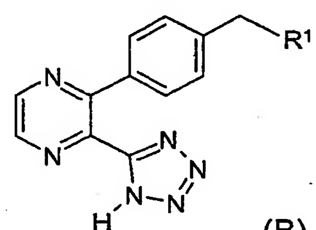
Claims

1. A compound library comprising or consisting of a set of structurally related compounds having core chemical structures (scaffolds) of the following general formulae



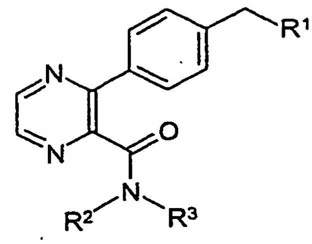
(A)

wherein the permitted substituents for R1 in compounds of formula A are dervived from the following precursor groups (List 1 and List 2), and # = point of attachment



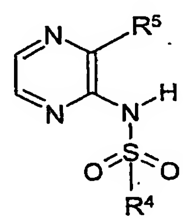
(B)

wherein the permitted substituents for R1 in compounds of formula B are derived from the following precursor groups (List 1 and List 2), and # = point of attachment



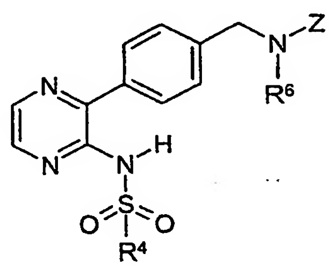
(C)

wherein the permitted substituents for R2R3N-# in compounds of formula C are derived from the following precursor groups (List 3), and # = the point of attachment



(D1)

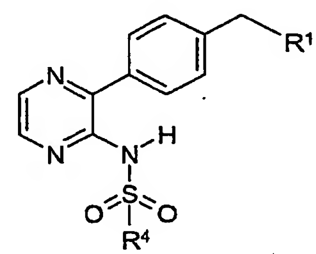
wherein the permitted substituents for $R4SO_2NH$-# in compounds of formula D1 are derived from the following precursor groups (List 5), and # = the point of attachment;
the permitted substituents for R5 in compounds of formula D1 are derived from the following precursor groups (List 7), and # = the point of attachment



(D2)

wherein the permitted substituents for R4SO_2NH-# in compounds of formula D2 are derived from the following precursor groups (List 5) and # = the point of attachment;

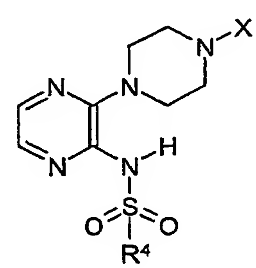
the permitted substituents for R6NZ-# in compounds of formula D2 are derived from the following precursor groups (List 4), and # = the point of attachment; and Z = H, Me, or an acyl or sulphonyl group derived from the following precursor groups (List 6)



(D3)

wherein the permitted substituents for R4SO_2NH # in compounds of formula D3 are derived from the following groups (List 5), and # = the point of attachment;

the permitted substituents for R1 in compounds of formula D3are derived from the following groups (List 1 and List 2), and # = the point of attachment



(E)

wherein the permitted substitunets for $R4SO_2NH$-# in compounds of formula E are derived from the following groups (List 5), and # = the point of attachment;

X is R7CO-#, $R8SO_2$-# or R9 or R10NHYC-# or R11 wherein

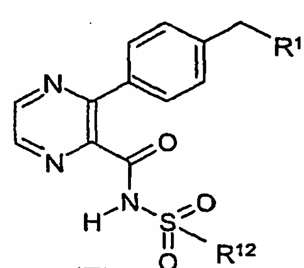
the permitted substituents for R7CO-# in compounds of formula E are derived from the following precursor groups (List 8), and # = the point of attachment;

the permitted substituents for $R8SO_2$-# in compounds of formula E are derived from the following precursor groupsd (List 9), and # = the point of attachment;

the permitted substituents for R9 in compounds of formula E are derived from the following precursor groups (List 11), and # = the point of attachment;

the permitted substituents for R10NHYC-# in compounds of formula E are derived from the following precursor groups (List 10), Y=O or S, and # = the point of attachment;

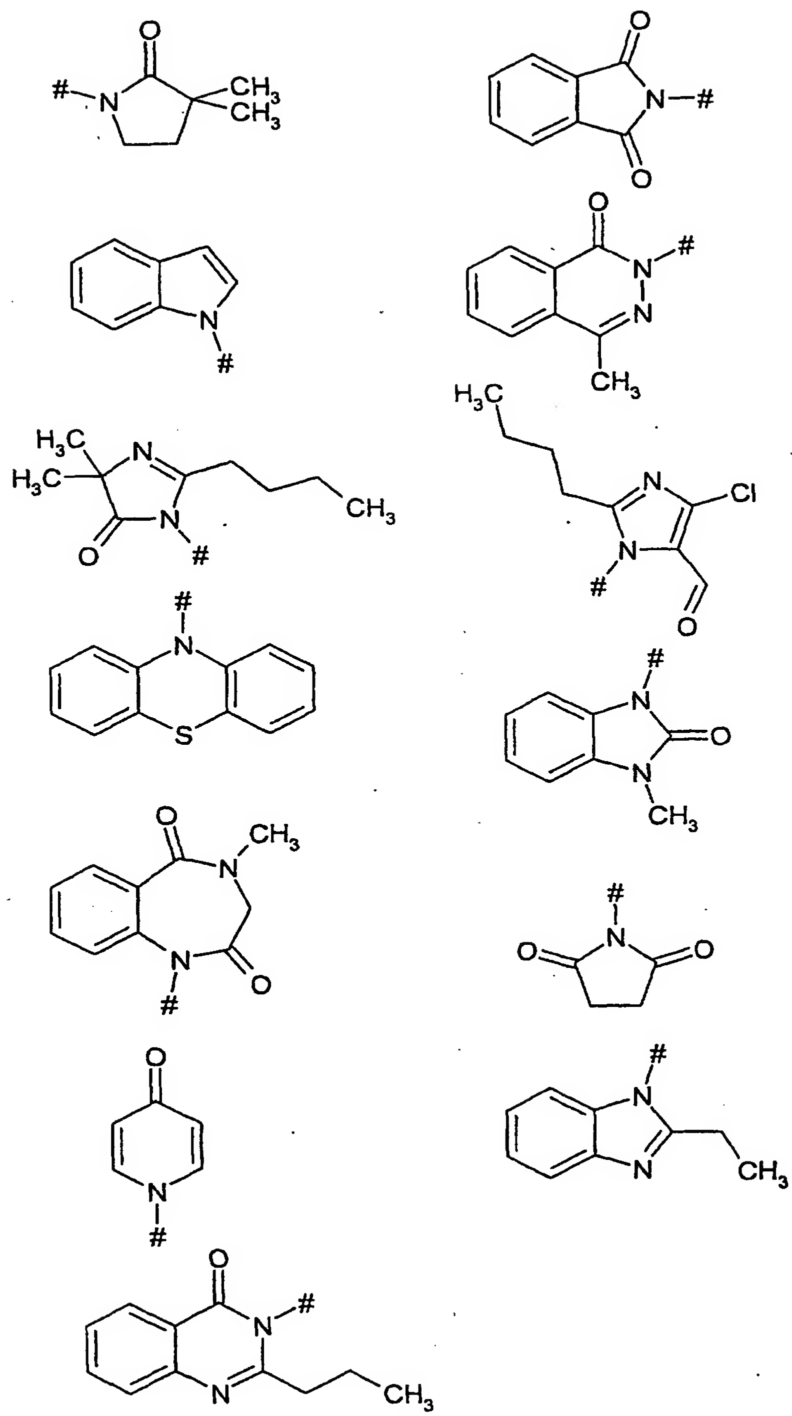
the permitted substituents for R11 in compounds of formula E are derived from the following groups (List 12), and # = the point of attachment



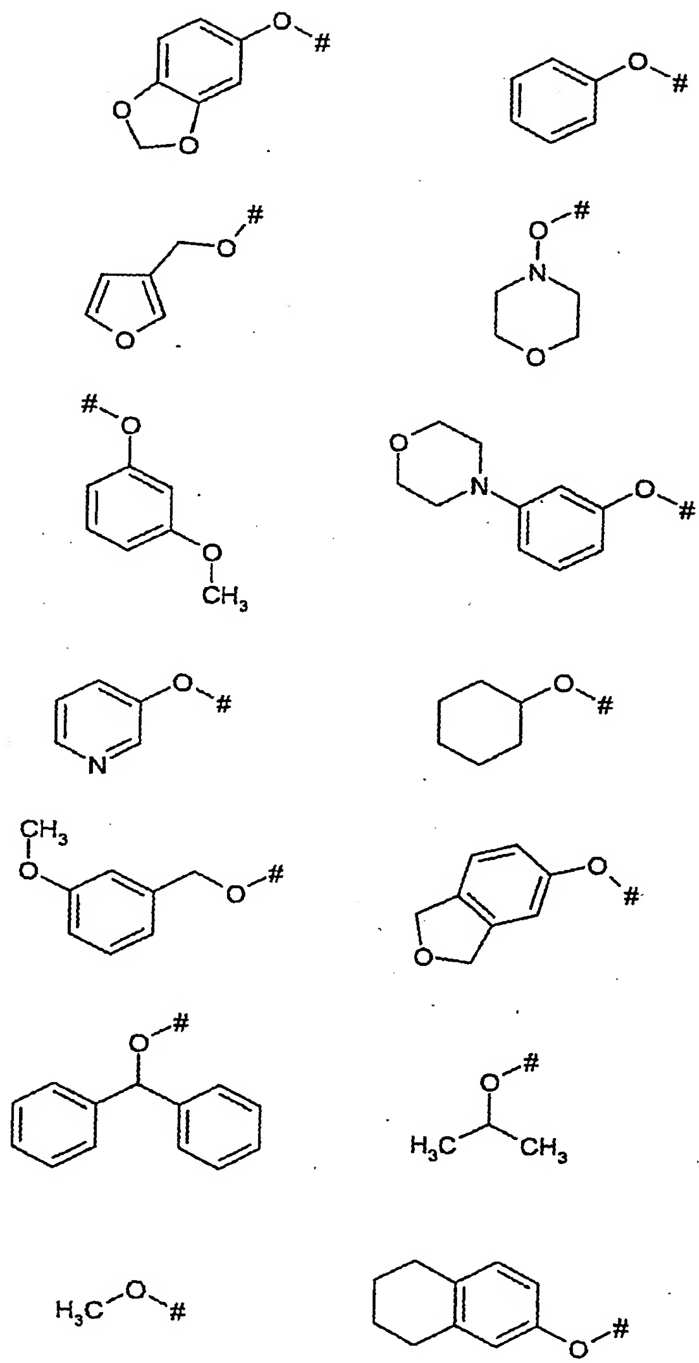
(F)

wherein the permitted substituents for $R12SO_2NH$-# in compounds of formula F are derived from the following groups (List 13), and # = the point of attachment.

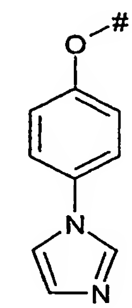
List 1 (R^1-#)

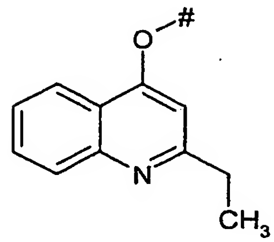


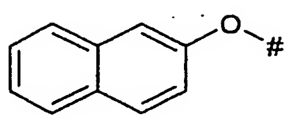
List 2 (R^1-#)

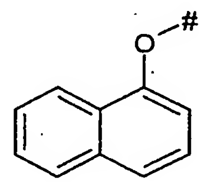


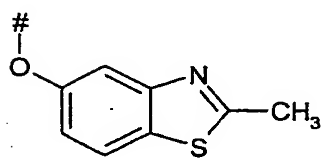
List 2 (Continued)

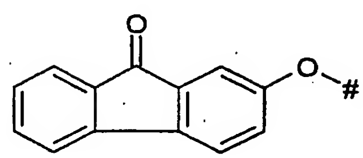


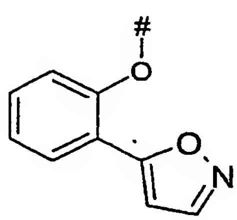




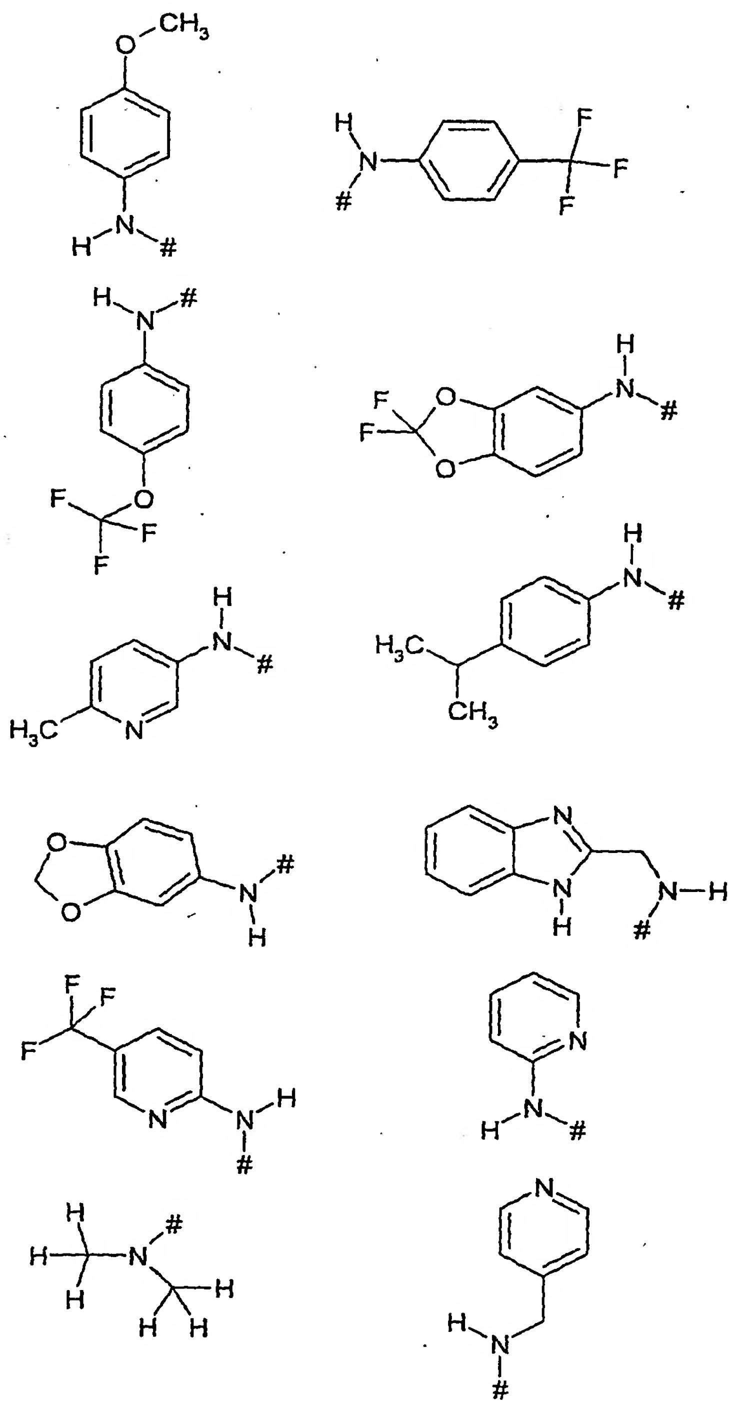




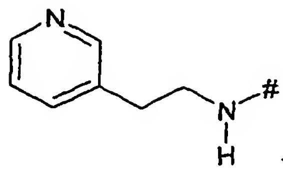
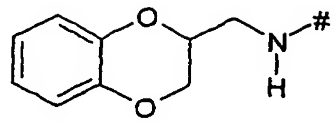
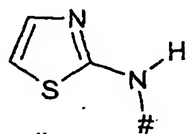
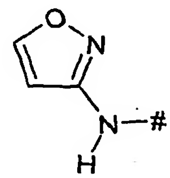
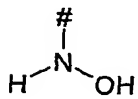
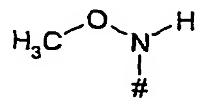
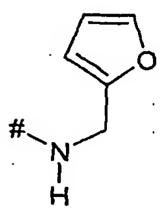
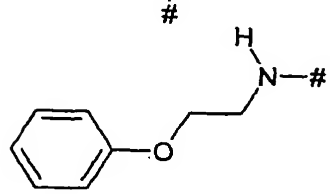
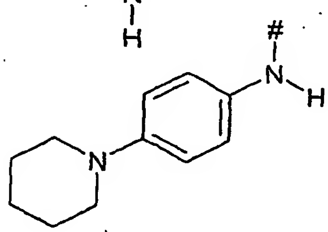
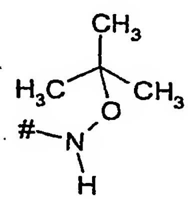
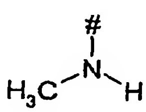
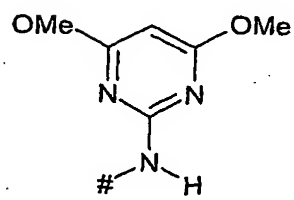
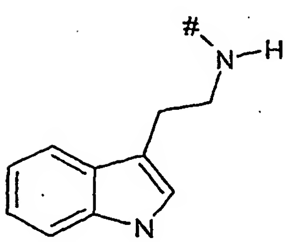
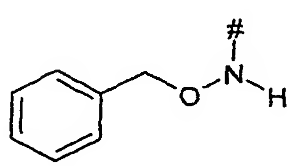




List 3 (R^2R^3N-#)



List 3 (Continued)

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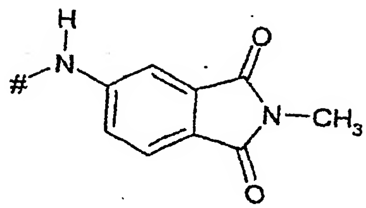

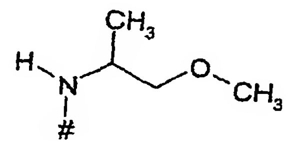

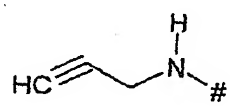

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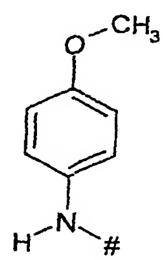

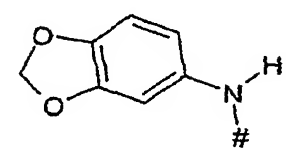

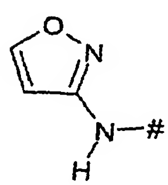

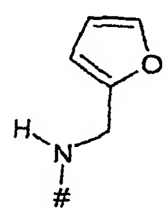

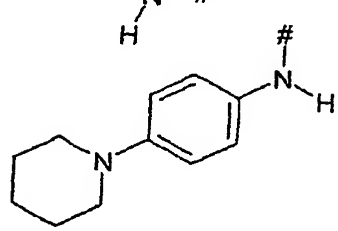

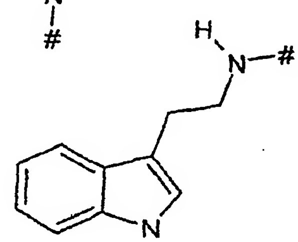

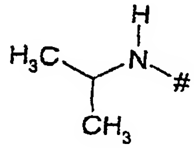

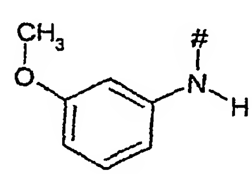

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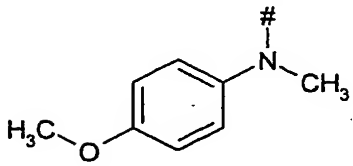
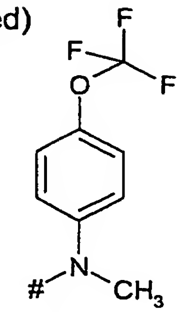
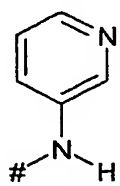
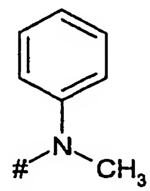
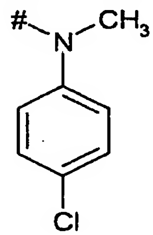
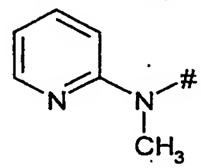
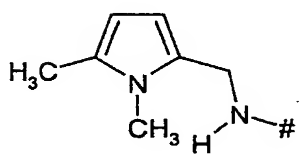
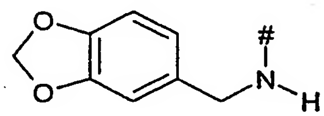
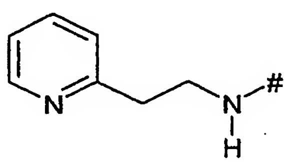
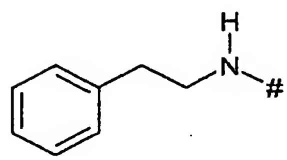
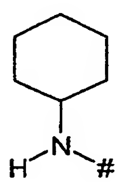
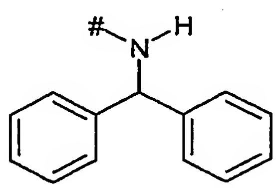
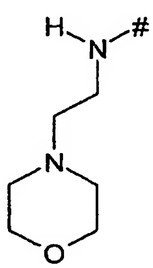
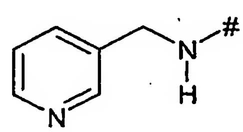
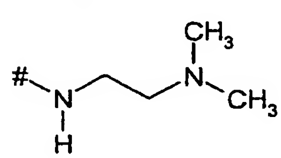

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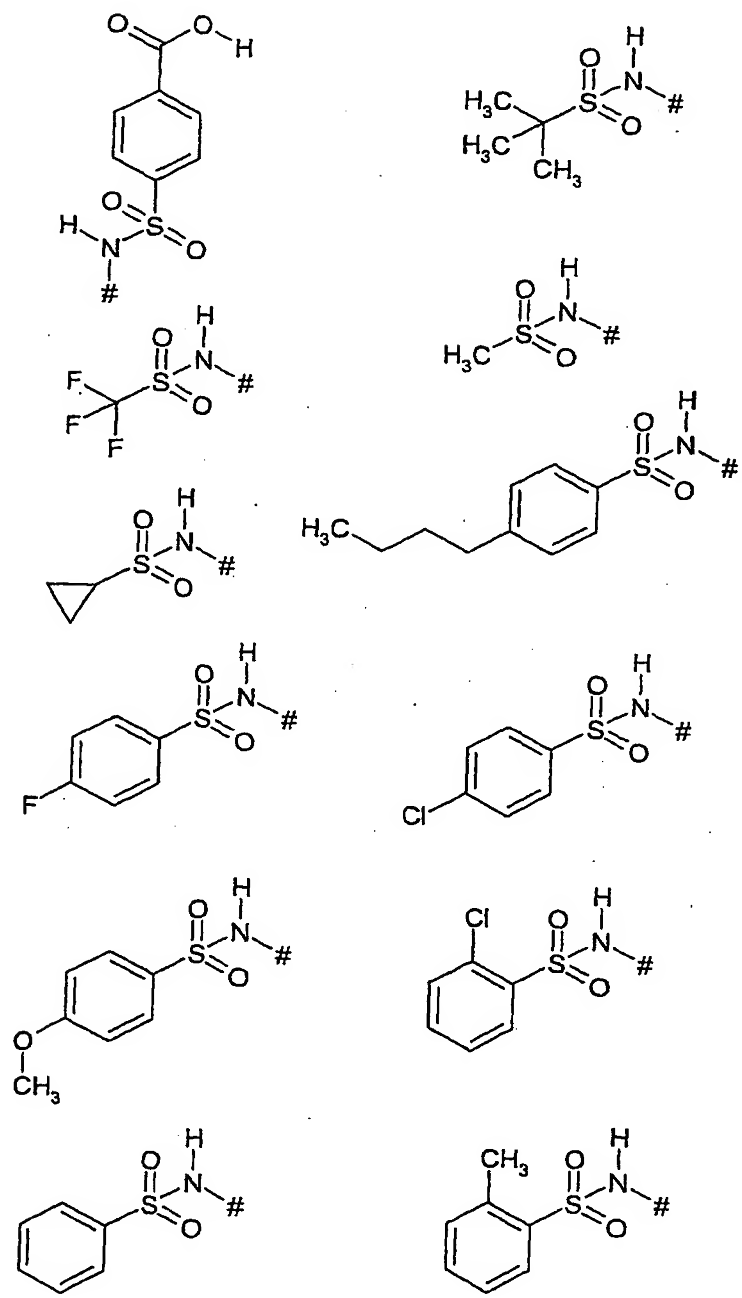

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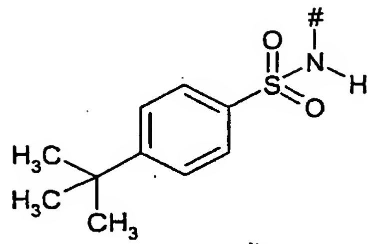

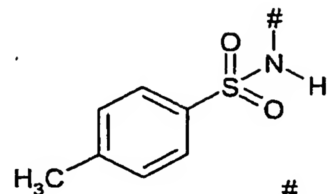

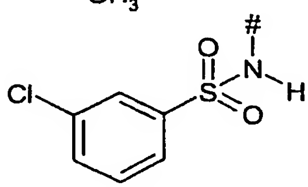

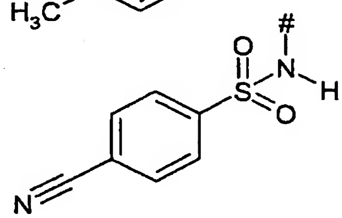

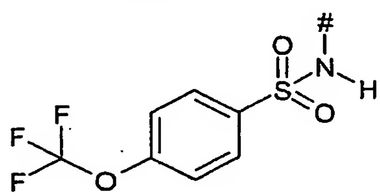

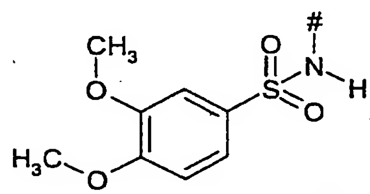

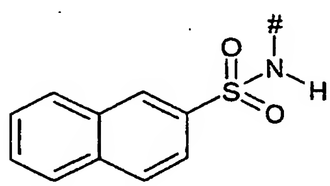

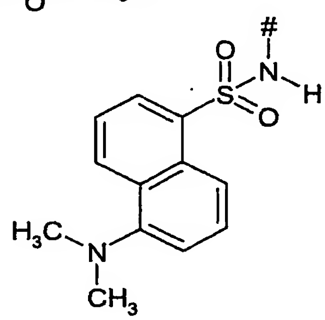

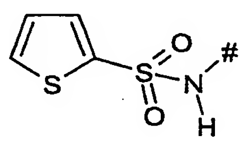

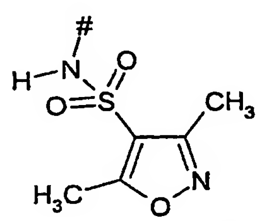

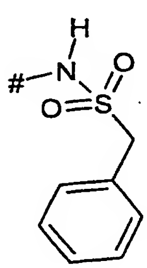

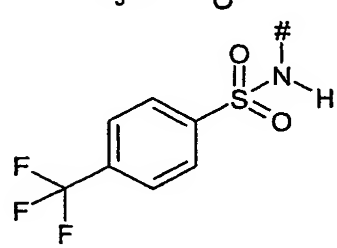

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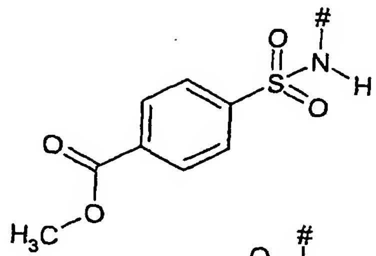

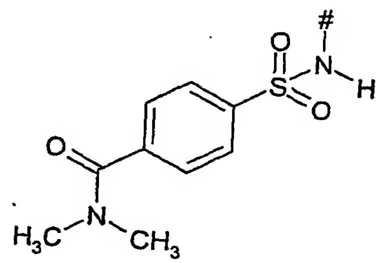

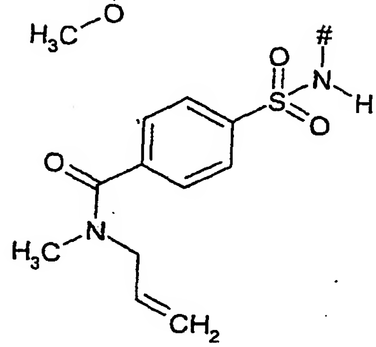

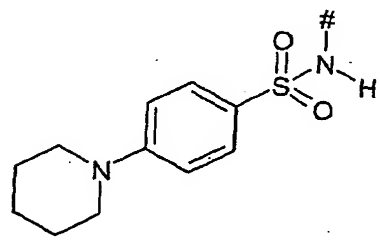

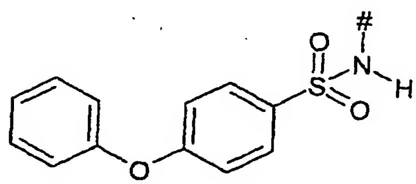

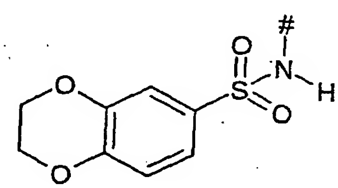

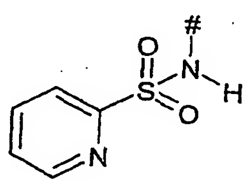

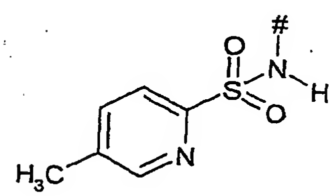

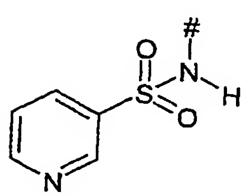

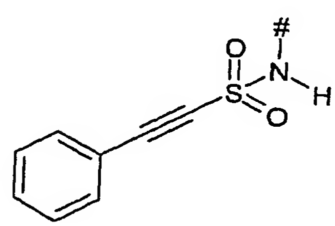

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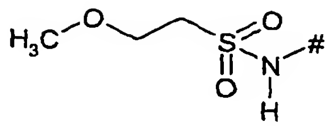

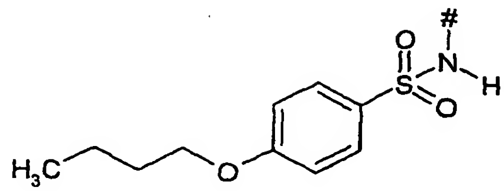

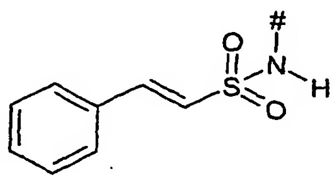

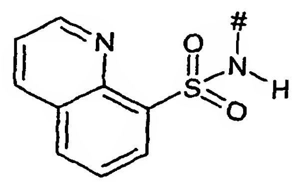

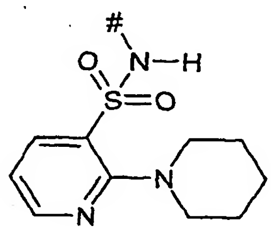

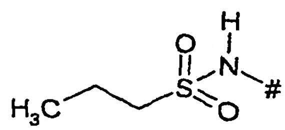

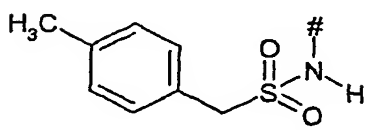

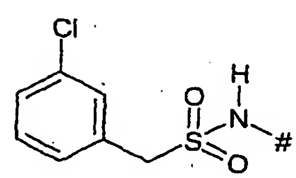

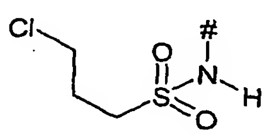

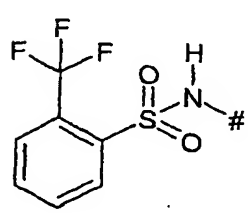

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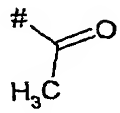

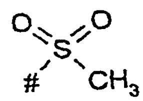

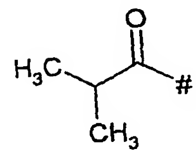

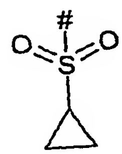

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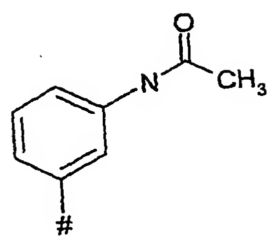

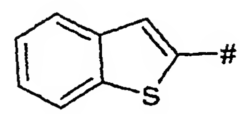

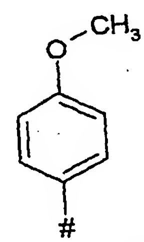

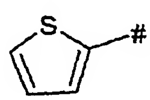

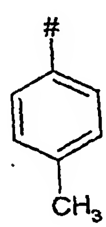

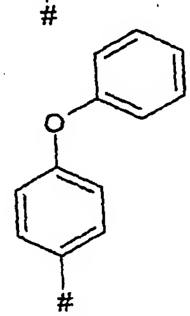

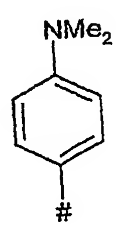

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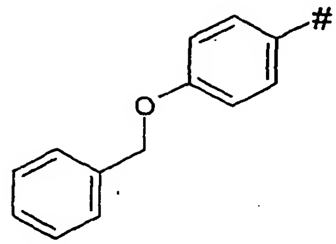
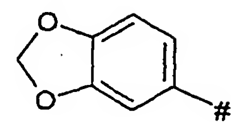
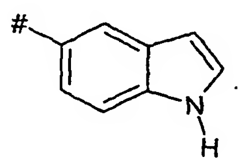
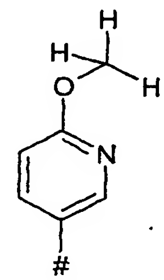
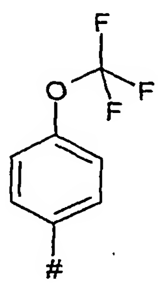
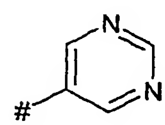


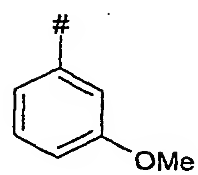


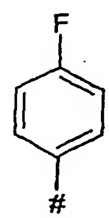


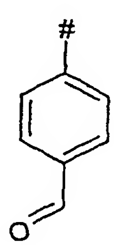


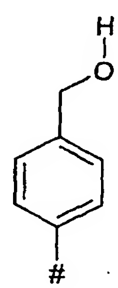




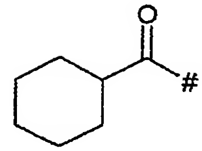
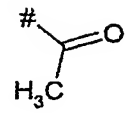
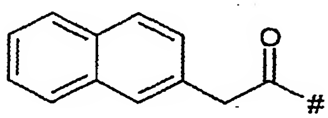
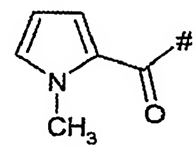
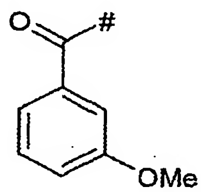
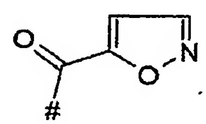
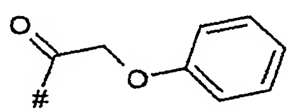
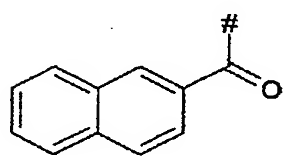
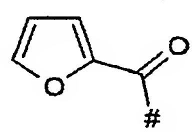
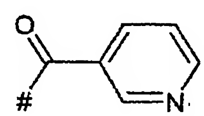
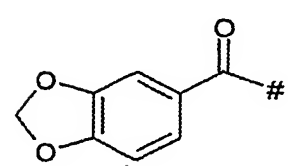
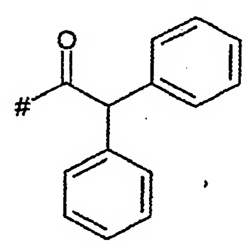
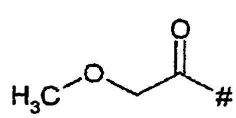
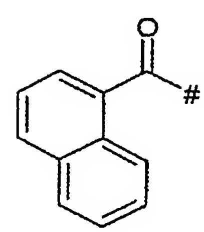








List 8 (R^7CO-#)

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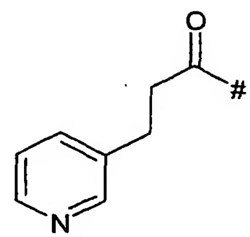
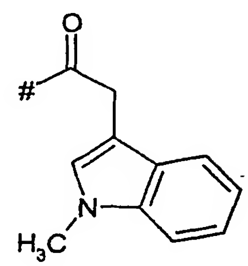
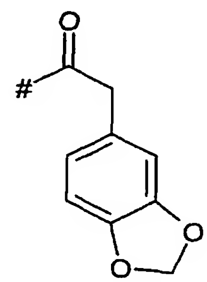
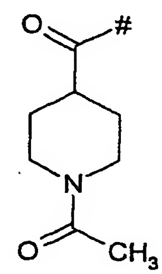
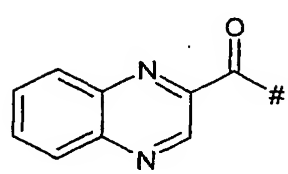
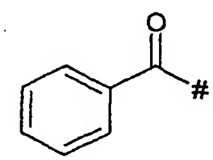


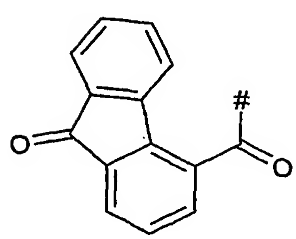


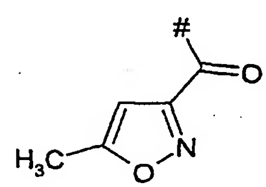


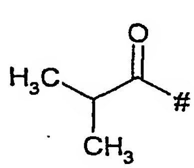




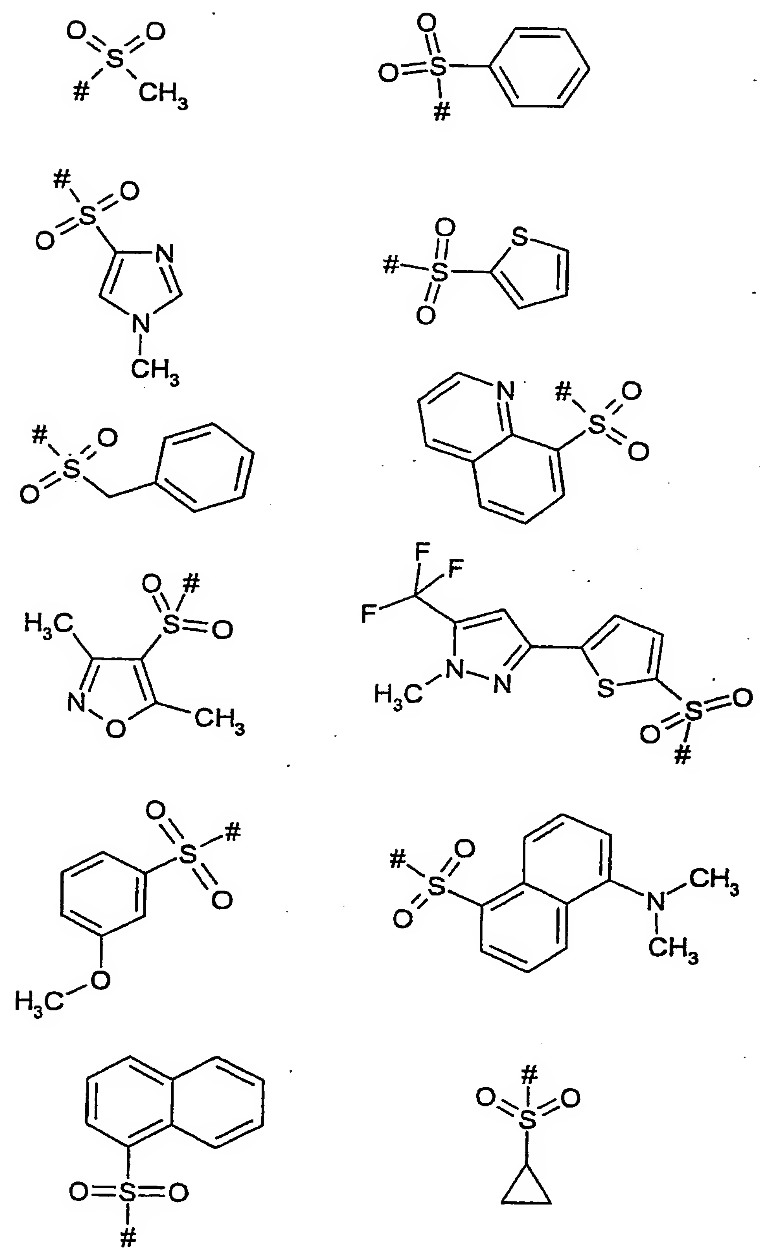








List 9 (R^8SO_2-#)



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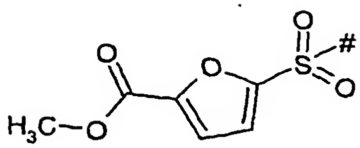
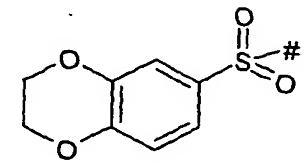
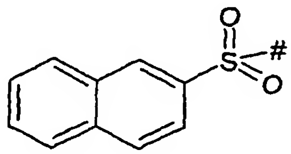
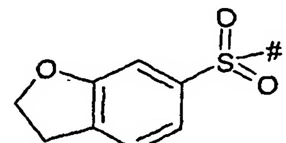
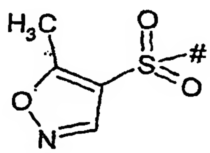
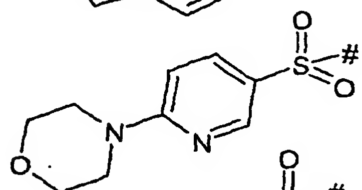


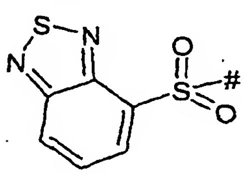


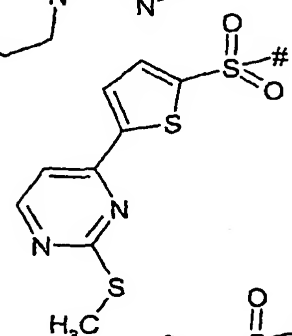


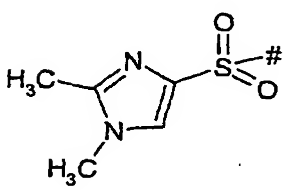


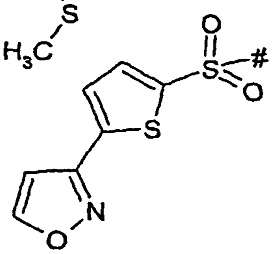


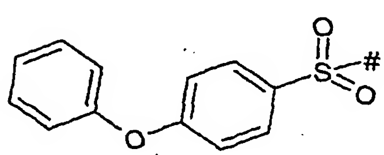


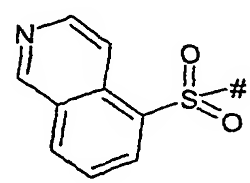




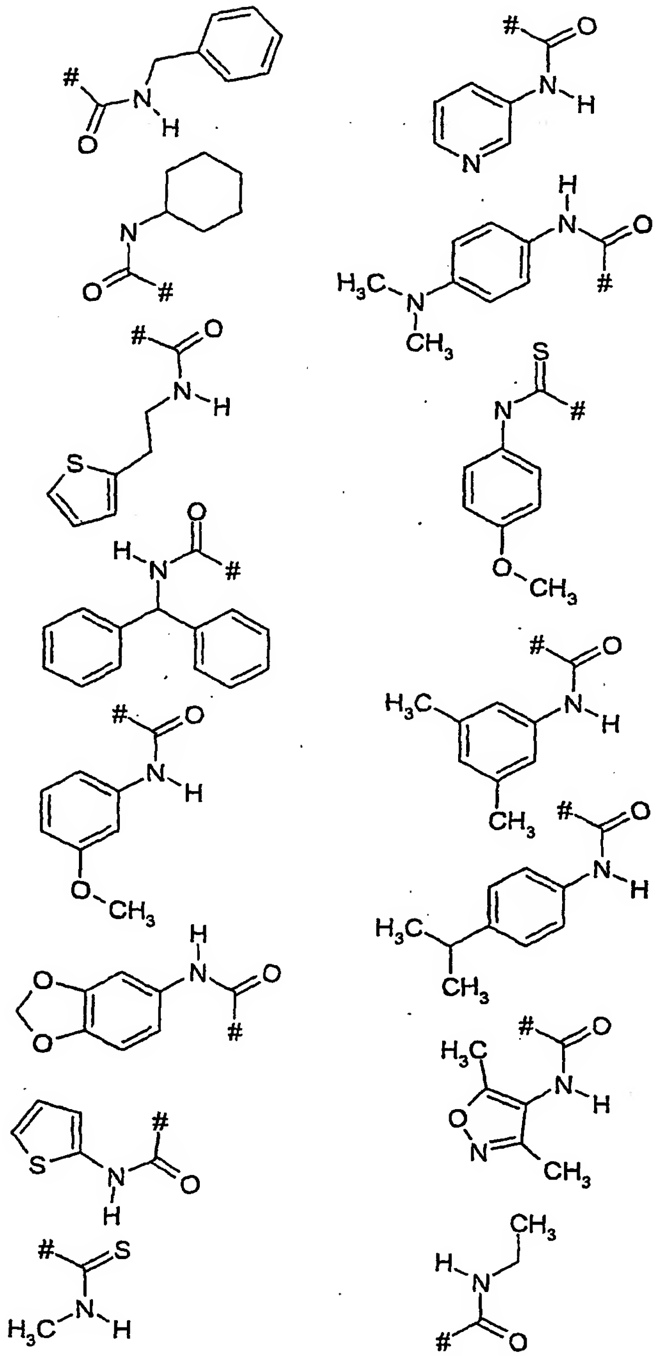




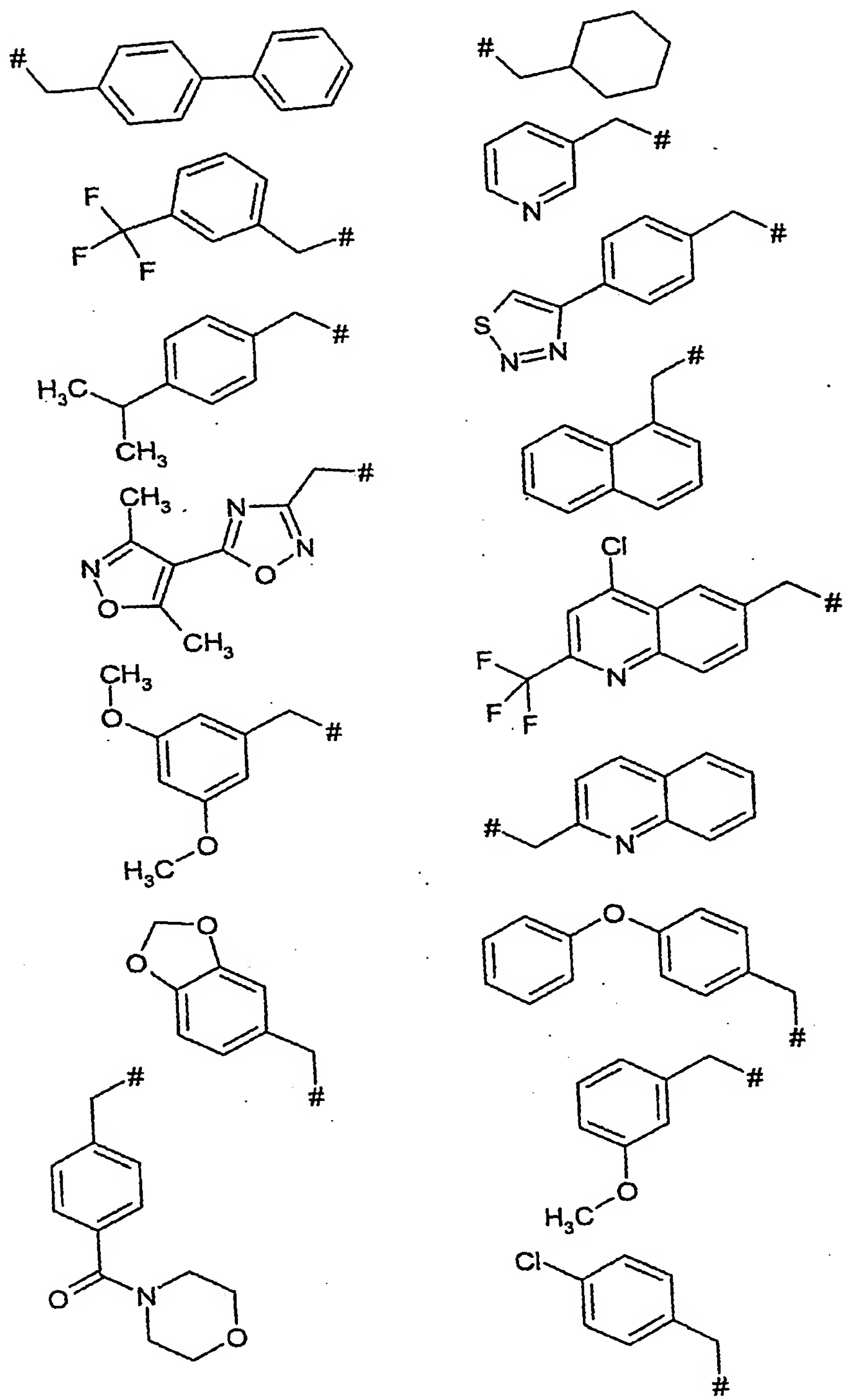




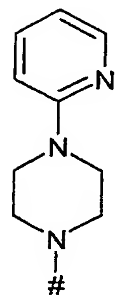
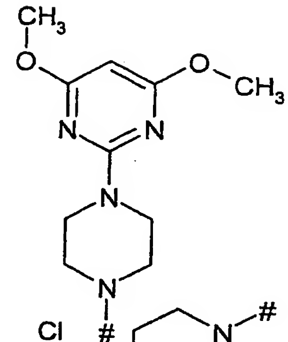
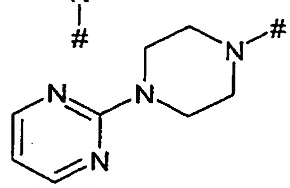
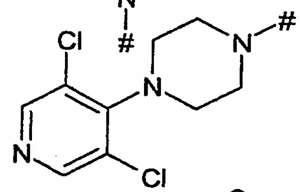
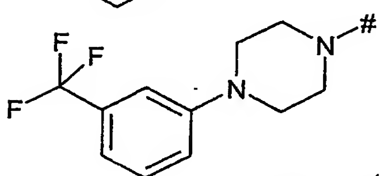
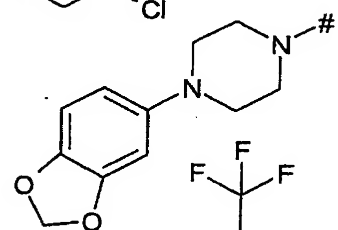
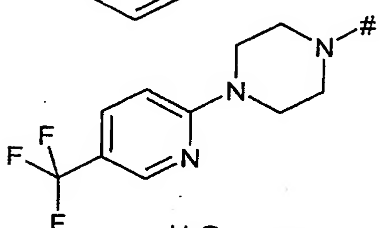
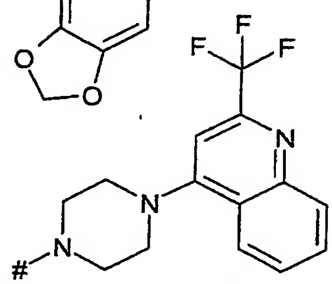
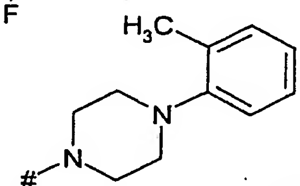
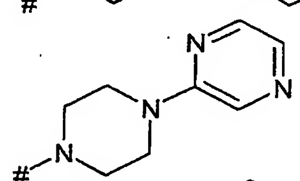
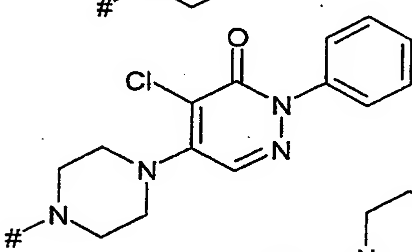
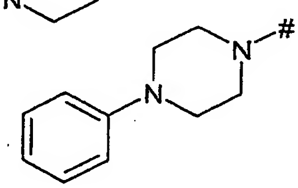
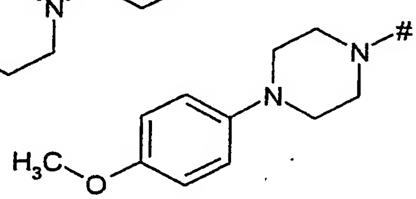
List 10 (R^{10}NHCO-#)



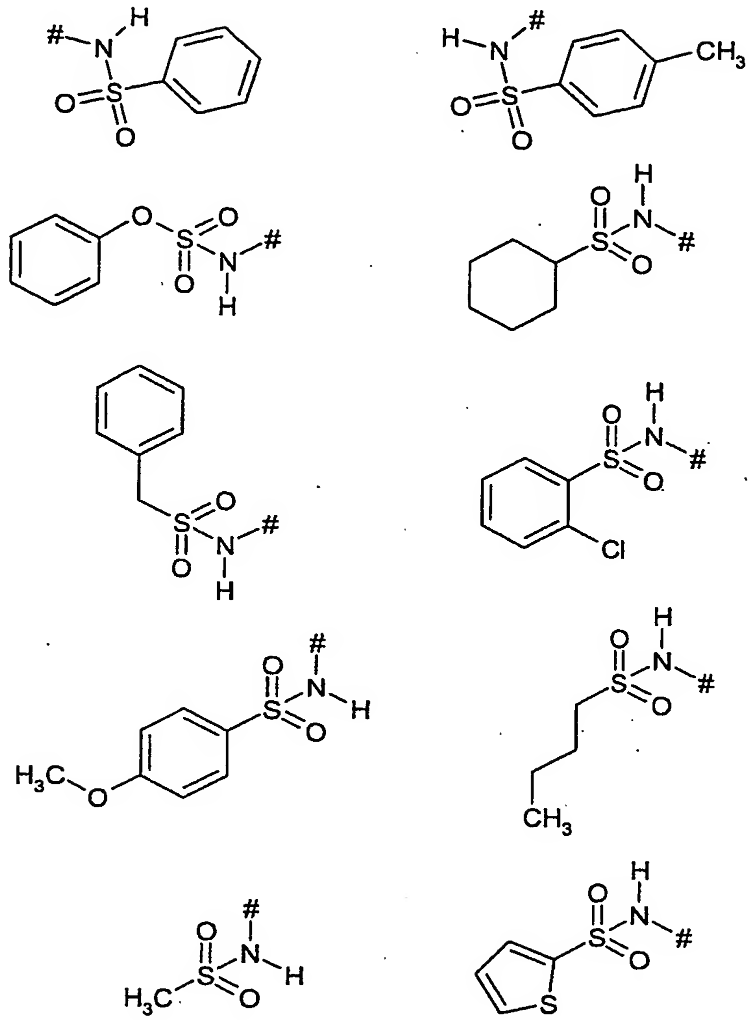
List 11 (R^9-#)



List 12 (R^{11}-#)

List 13 ($R^{12}SO_2NH$-#)

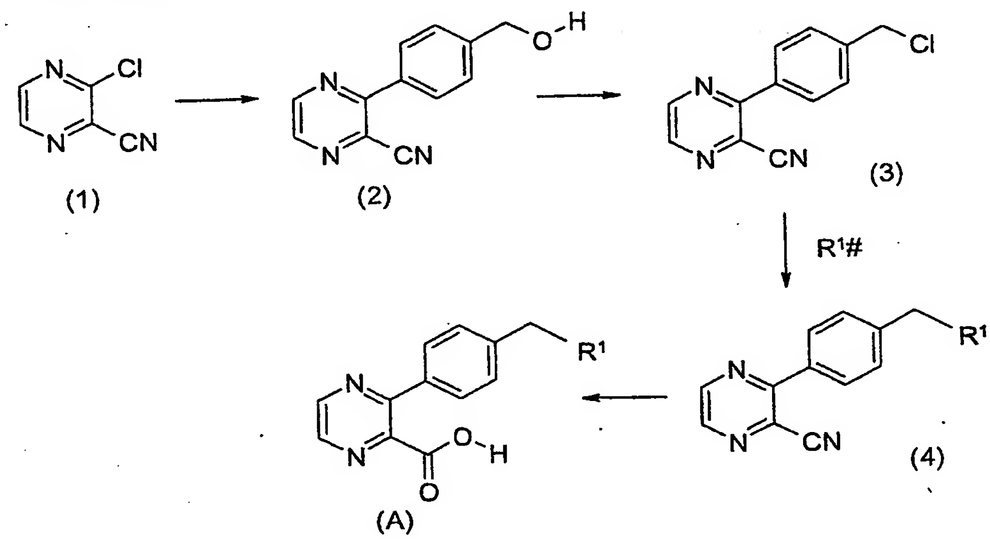


2. A library according to claim 1 wherein said library has all or substantially all of the compounds represented therein.

3. A library according to claim 1 or 2 wherein said library has about 100, 1000, 2000, 3000, or 10,000 of the compoounds represented therein.

4. A method of making a compound library according

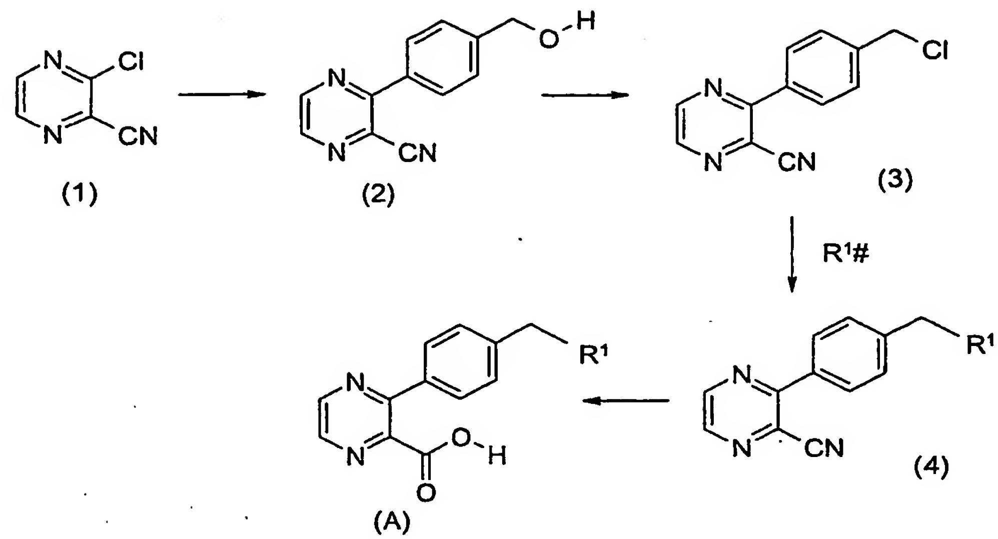
to claim 1, which method comprises the step of synthesising compounds of formula A according to the following reaction scheme:



(Scheme1)

wherein R1 is as defined in claim 1.

5. A method of making a compound library according to claim 1, which method comprises the step of synthesising compounds of formula A according to the following reaction scheme:



(Scheme1)

wherein (1) is coupled to 4-hydroxymethyl benzyene boronic acid;

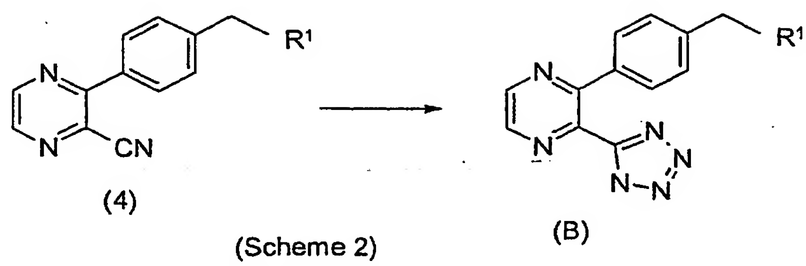
the resultant benzyl alcohol (2) is converted to the benzyl chloride (3) and thionyl chloride;

the benzyl chloride is reacted with a range of nucleophiles (R1-# from List 1 or List 2 where #=H) to give carbonitriles (4) (R1-# is from List 1 or List 2 and #=the point of attachment); and

the resultant carbonitriles (4) are hydrolysed to give acids (A);

and Lists 1 and 2 are as defined in claim 1.

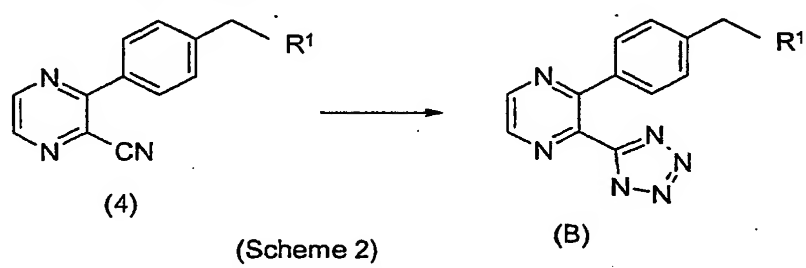
6. A method for making a compound library according to claim 1, which method comprises the step of synthesising compounds of formula B according to the following scheme:



(Scheme 2)

wherein R1 is as defined in claim 1.

7. A method for making a compound library according to claim 1, which method comprises the step of synthesising compounds of formula B according to the following scheme:

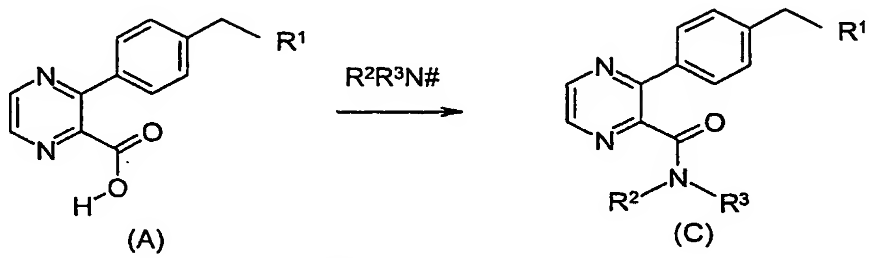


(Scheme 2)

wherein (1) is coupled to 4-hydroxymethyl benzene boronic acid;
the resultant benzyl alcohol (2) is converted to the benzyl chloride (3) and thionyl chloride;
the benzyl chloride is reacted with a range of nucleophiles (R1-# from List 1 or List 2 where #=H) to give carbonitriles (4) (R1-# is from List 1 or List 2, where #=the point of attachment);
the resultant carbonitriles (4) are converted to the tetrazoles (B) with trimethylsilyl azide;and
Lists 1 and 2 are as defined in claim 1.

8. A method for making a compound library according to claim 1, which method comprises the step of synthesising compounds of formula A according to claim 4 and further reacting these compounds to give

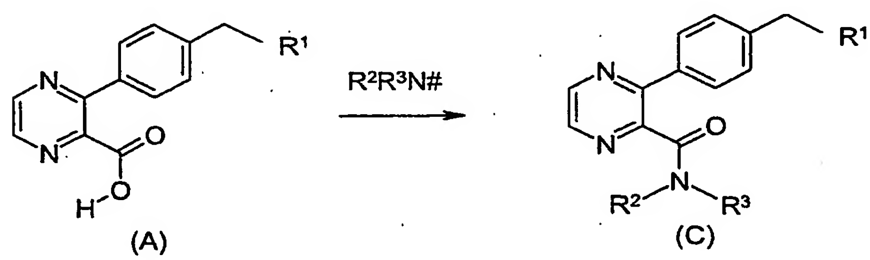
compounds of formula C according to the following scheme:



(Scheme 3)

wherein R2, and R3 are as defined in claim 1.

9. A method for making a compound library according to claim 1, which method comprises the step of synthesising compounds of formula A according to claim 4 and further reacting these compounds to give compounds of formula C according to the following scheme:



(Scheme 3)

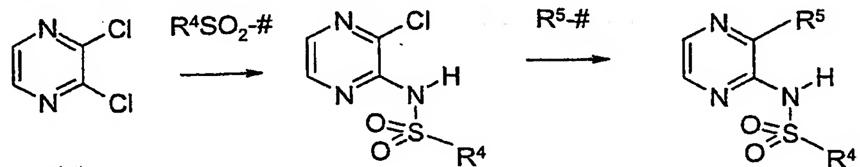
wherein the acids of formula A are reacted with oxalyl chloride;

the resultant acid chlorides are reacted with amines (R2R3N-# from List 3, where #=H) to give amides of formula C (R2R3N-# from List 3, where # = the point of attachment);and

List 3 is as defined in claim 1.

10. A method for making a compound library

according to claim 1, which method comprises the step of synthesising compounds of formula D1 according to the following reaction scheme:

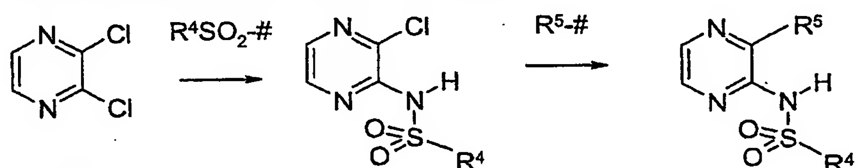


(5) (6) (D1)

(Scheme 4a)

wherein R4, and R5 are as defined in claim 1.

11. A method for making a compound library according to claim 1, which method comprises the step of synthesising compounds of formula D1 according to the following reaction scheme:

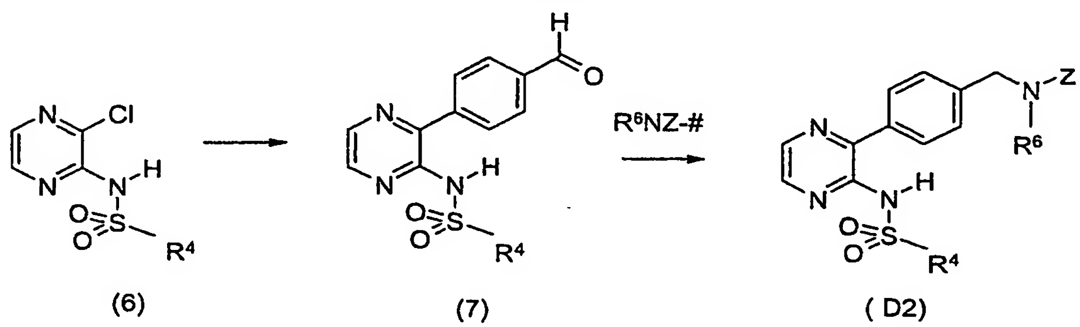


(5) (6) (D1)

(Scheme 4a)

wherein 2,3 - dichlocopyrazine (5) is reacted with sulphonic acid amides (R4SO$_2$NH-# from List 5 where # = H);
the resultant sulphonic acid (3-chloropyrazin-2-yl) amides (6) are coupled with a range of aromatic or heteroaromatic boronic acids (R5-# from List 7 where #=B(OH)$_2$) to give sulphonic acid amides of formula D1 (R4SO$_2$NH-# is from List 5, where #=the point of attachment, and R5-# is from List 7, where # = the point of attachment); and
Lists 5 and 7 are as defined in claim 1.

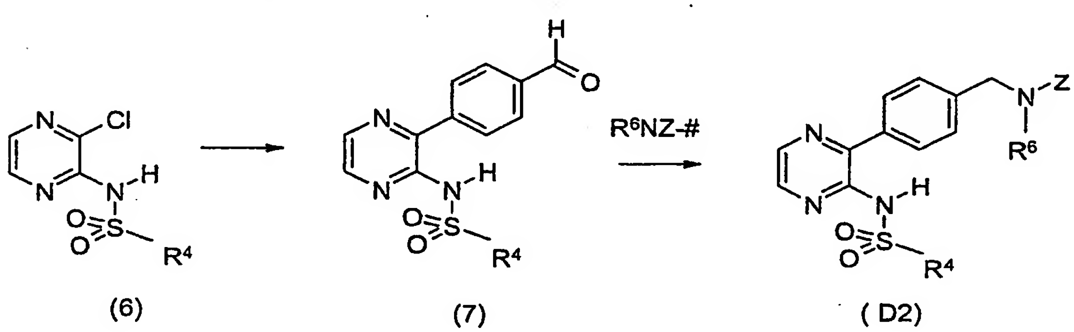
12. A method for making a compound library according to claim 1, which method comprises the step of synthesising compounds of formula D2 according to the following reaction scheme.



(Scheme 4b)

wherein R4 and R6 are as defined in claim 1.

13. A method for making a compound library according to claim 1, which method comprises the step of synthesising compounds of formula D2 according to the following reaction scheme.

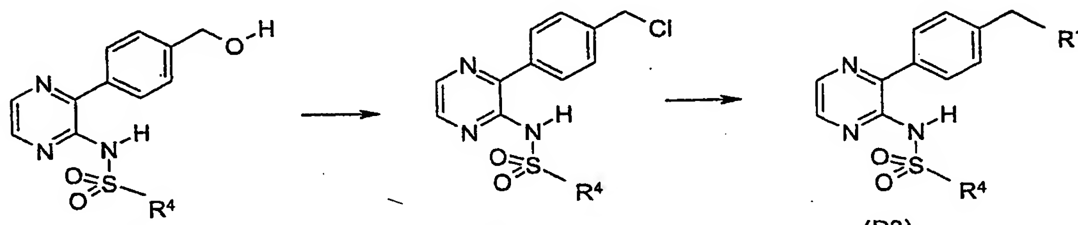


(Scheme 4b)

wherein 2,3-dichloropiazine is reacted with sulphonic acid amides (R4SO_2NH-# from List 5, where #=H); the resultant sulphoic acid (3-chloropyrazine-2-yl) amides (6) are coupled with 4-formyl benzene boronic acid; the resultant aldehydes are converted to benzylamines (D2) (R6NZ-# is from List 4, Z=H or Me, and # the point

of attachment) by reductive amination with amines (R6NZ-H from List 4 where Z=H or me, and #=H); compounds of formula D2, where Z=H, may then optionally be reacted with chlorides or sulphonyl chlorides in the presence of a base to give amides and sulphonamides of formula D2a, where Z=acyl or sulphonyl from List 6 and #=the point of attachment;
Lists 4 and 5 are as defined in claim 1.

14. A method for making a compound library according to claim 1, which method comprises the step of synthesisisng compounds of formula D3 according to the following reaction scheme:

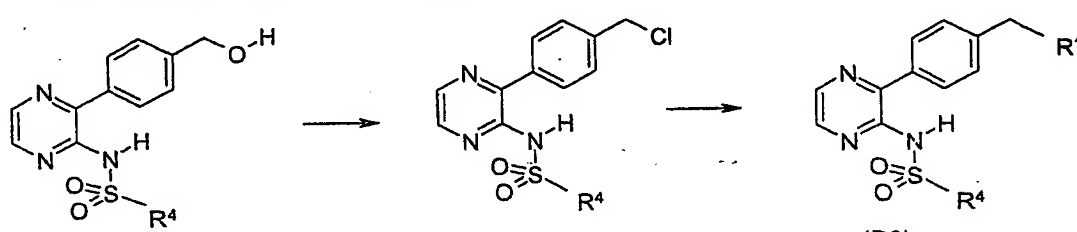


(8) (9) (D3)

(Scheme 4c)

wherein R4 and R1 are as defined in claim 1.

15. A method for making a compound library according to claim 1, which method comprises the step of synthesisisng compounds of formula D3 according to the following reaction scheme:

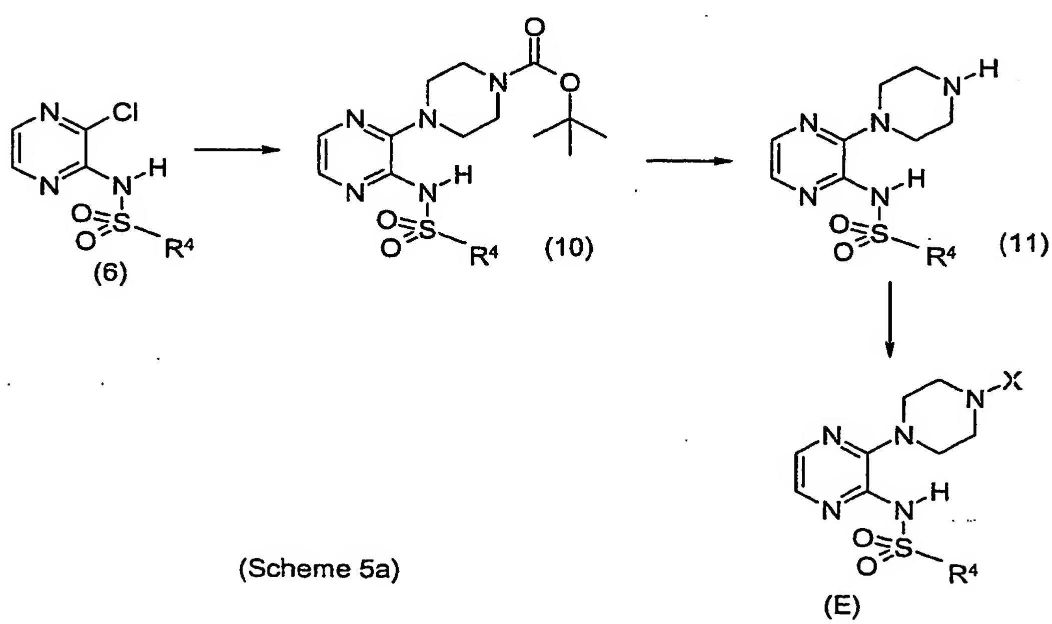


(8) (9) (D3)

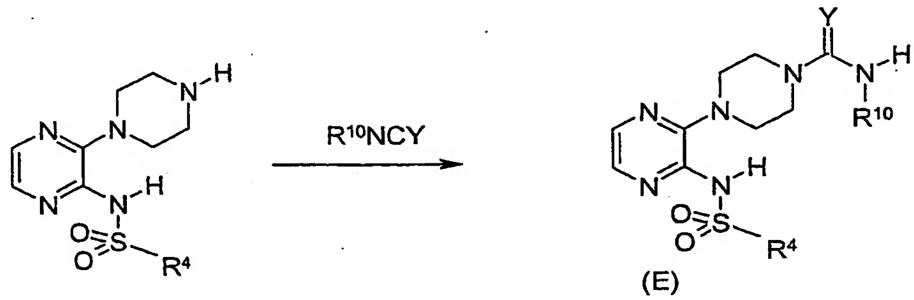
(Scheme 4c)

wherein 2,3 - dichloropyrazine is reacted with sulphonic acid amides ($R4SO_2$ NH-# from List 5, where #=H);
the resultant sulphonic acid (3-chloropyrazine-2-yl) amides are coupled with 4-hydroxymethyl phenyl boronic acid;
the resultant benzyl alcohols (8) are converted to benzyl chlorides (9) with thionyl chloride;
the benzyl chlorides are reacted with a range of nucleophiles (R1-# from List 1 and List 2 where #=H) to give compounds of formula D3 (R1-#is from List 1 and List 2, where #=the point of attachment); and
Lists 1 and 2 are as defined in claim 1.

16. A method for making a compound library according to claim 1, which method comprises the step of synthesising compounds of formula E according to the following reaction schemes:

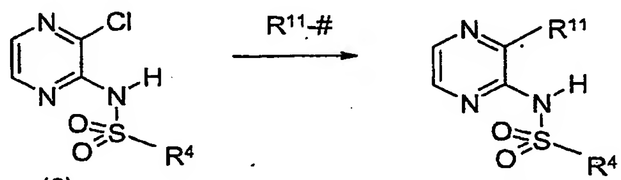


(Scheme 5a)



(11) (E)

(Scheme 5b)

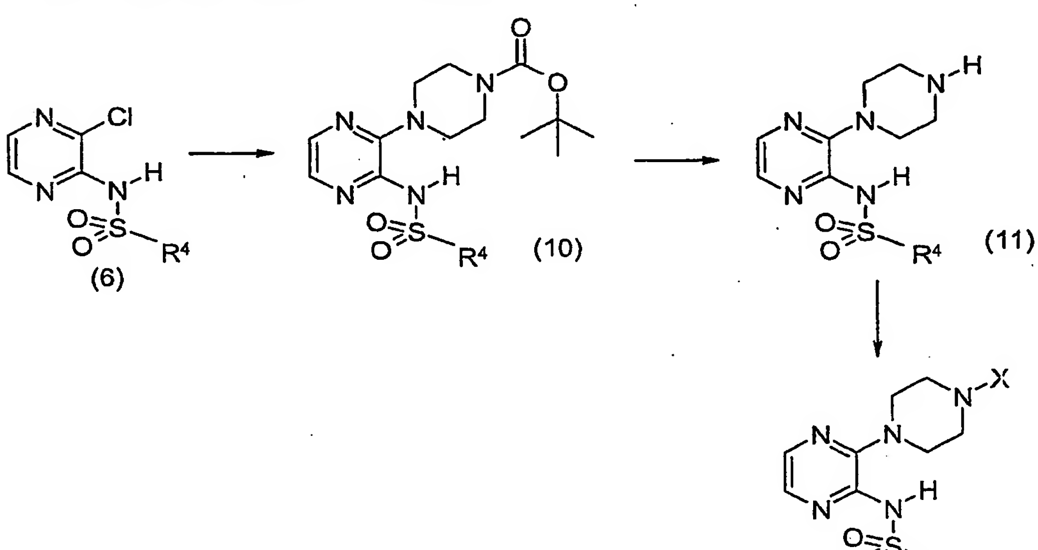


(6) (E)

(Scheme 5c)

wherein R4, R10, R11 and X are as defined in claim 1.

17. A method for making a compound library according to claim 1, which method comprises the step of synthesising compounds of formula E according to the following reaction scheme:

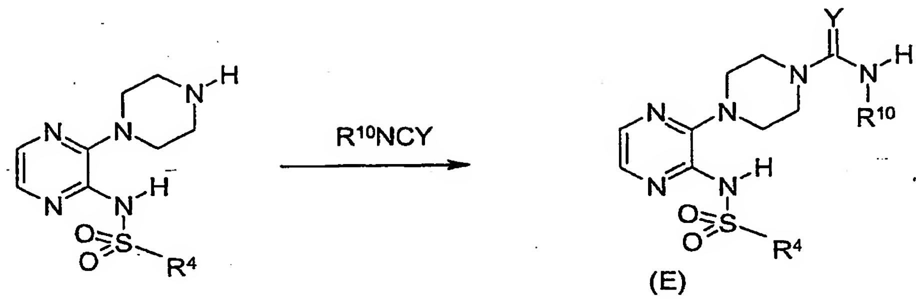


(6) (10) (11) (E)

(Scheme 5a)

wherein 2,3 - dichloropyrazine is reacted with sulphonic acid amides ($R4SO_2NH$-# from List 5, where #=H);
the resultant sulphonic acid (3-chloropyrazin-2-yl) amides (6) are reacted with piperazine-1-carboxylic acid tert-butyl ester;
the resultant compounds (10) are treated with a suitable acid to remove the tert-butyl groups;
the resultabt piperazines (11) are reacted with:
acid chlorides (R^7CO-# from List 8, where #=Cl) to give compounds of formula E where X=R7CO-# from List 8 and #= the point of attachment
sulphonyl chlorides ($R8SO_2$ -# from List 9, where #=Cl) to give compounds of formula E where $R8SO_2$-# from List 9 and #= the point of attachment
alkyl halides (R9-# from List 11, where #=halogen) to give compounds of formula E nwhere R9-# from List 11 and #= the point of attachment
isocyanates or isothiocyanates (RIONHYC-# from List 10, where Y=O or S) to give compounds of formula E where RIONHYC-# from List 10 (Y=O or S) and #= the point of attachment
1-heterocacyl or 1-aryl piperazines (R11-# from List 12 where #=H) to give compounds of formula E where R11-# from List 12 and #= the point of attachment) ; and
Lists 5, 8, 9, 10, 11 and 12 are as defined in claim 1.

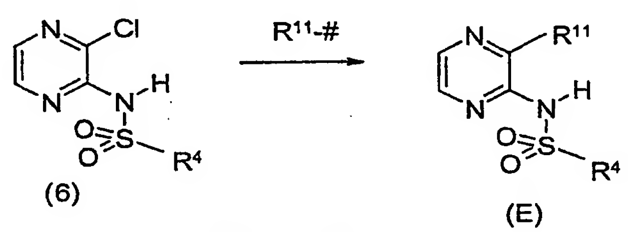
18. A method for making a compound library according to claim 1, which method comprises the step of synthesising compounds (11) according to claim 10 and further reacting these compounds to give compounds of formula E according to the following reaction scheme:



(11) (Scheme 5b)

wherein the piperazines (11) are reacted with isocyanates and isothiocyanates (R10=N=Y from List 10, where Y = O or S) to give ureas and thioureas of formula e (R10NHCY-# from List 10, where # = the point of attachment) ; and
List 10 is as defined in claim 1.

19. A method for making a compound library according to claim 1, which method comprises the step of synthesising compounds of formula E according to the following reaction scheme:

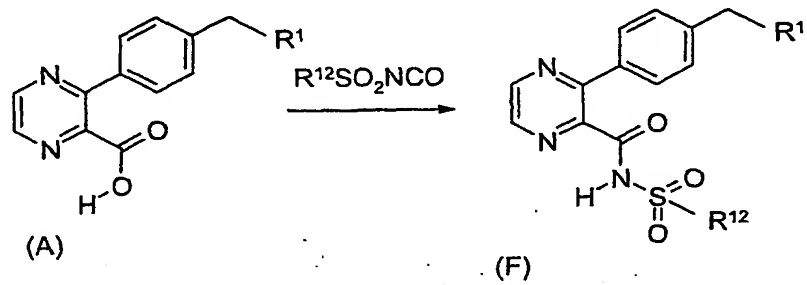


(Scheme 5c)

wherein sulphonic acid (3-chloroyrazines-2-yl) amides (6) are heated with 1-heteroaryl or 1-aryl piperazines (R^{11}-# from List 12, where # = H) to give compounds of formula E directly (R^{11}-# from List 12, where # = point of attachment) ; and
List 12 is as defined in claim 1.

20. A method for making a compound library according to claim 1, which method comprises the step

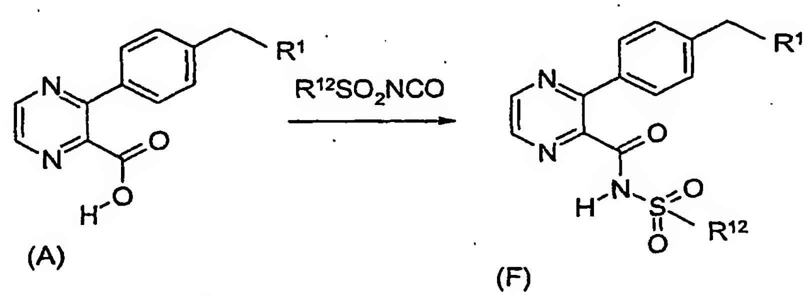
of synthesising compounds of formula A according to claim 4 and further reacting these compounds to give compounds of formula F according to the following reaction scheme:



(Scheme 6)

wherein R1 and R12 are as defined in claim 1.

21. A method for making a compound library according to claim 1, which method comprises the step of synthesising compounds of formula A according to claim 4 and further reacting these compounds to give compounds of formula F according to the following reaction scheme:



(Scheme 6)

wherein acids of formula (A) are reacted with sulphonyl isocyanates (RI2SO_2NCO from List 13) in the presence of a base to give compounds of formula F (RI2SO_2NH-# from List 13, where #=the point of attachment) ; and List 13 is as defined in claim 1.

22. A method for making a compound library according to claim 1, which method is according to any or all of the steps of claims 4-21.

23. A method for making a compound library according to claim 1, which method further comprises the step of forming the intermediate compounds (2), (3) and (4) according to the method of claim 4.

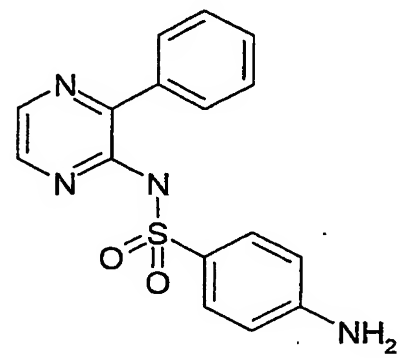
24. A method for making a compound library according to claim 1, which method further comprises the step of forming the intermediate compounds (6) according to the method of claim 10.

25. A method for making a compound library according to claim 1, which method further comprises the step of forming the intermediate compounds (7) according to the method of claim 12.

26. A method for making a compound library according to claim 1, which method further comprises the step of forming the intermediate compounds (8) and (9) according to the method of claim 14.

27. A method for making a compound library according to claim 1, which method further comprises the step of forming the intermediate compounds (10) and (11) according to the method of claim 16.

28. A compound capable of binding to a G-protein coupled receptor, which compound is selected from compounds represented within a library according to claim 1 but not including compounds having any of the following structures:



29. A method of making a compound according to claim 28, which method is according to the methods of claims 4 to 21.

30. A compound library comprising or consisting of a set of structurally related compounds, substantially as herein described.

31. A compound capable of binding to a G-protein coupled receptor, substantially as herein described.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/05668

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4965 A61K31/497 C07D241/24 C07D241/20 C07D241/22
C07D403/04 C07D401/12 C07D403/10 C07D413/12 C07B61/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98/54116 A (CADUS PHARMACEUTICAL CORP (US)) 3 December 1998 (1998-12-03) page 4, line 4 page 8, line 27 ---	1-31
A	WO 96/03424 A (SCRIPPS RESEARCH INST (US)) 8 February 1996 (1996-02-08) page 1, line 2 figures 17G,18D,19A,19D,20B examples 11,16,21,24,30 ---	1-31

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
22 April 2004	07/05/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cortés, J

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; PALAMIDASSI, G.: "Pyrazine derivatives. VI" retrieved from STN Database accession no. 59:75305 XP002277788 abstract & FARMACO, EDIZIONE SCIENTIFICA (1963), 18(8), 557-65 ,	1-31
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P,A	WO 03/031406 A (IRM LLC (US)) 17 April 2003 (2003-04-17) the whole document	1-31
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Int· ̄ ɔnal Application No
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